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THE TREATMENT OF ACUTE STOMATITIS

CHARLES HENDEE SMITH, M.D., NEW YORK, N. Y., AND
HERBERT B. JOHNSON, M.D., KINGSTON, N. Y.

THE classification and nomenclature of acute stomatitis is much confused. Different medical and dental writers use the same term for different conditions. Black[1] points out that over thirty terms are in use for the same disease. There are two common acute inflammatory conditions, aside from thrush.

The first is the ordinary "canker sore" which is usually preceded by a vesicle, although the ulcer may be the first lesion noticed. These are single or multiple, on the tongue, floor of the mouth, lips, or cheeks. There are no constitutional symptoms. At times canker sores are accompanied by labial herpes. They last from three to five days and are sometimes deep and painful. Some persons seem to be especially susceptible and have recurrences throughout life, from the same factors which cause herpes, e.g., indigestion, fever, and menstruation. Obviously, no immunity develops, even from repeated attacks. This form is often called herpetic stomatitis.

The second is an acute disease seen mostly in young children between 1 and 3 years, but occurring also in older children and even up to adult life, sporadically or in epidemics in families, schools, or armies. It begins with fever, severe general aches, pains, and prostration. The patient feels really ill for several days. After a day or two of fever, inflammatory lesions are noted in the mouth, at first with swelling and redness, and then shallow ulceration. These lesions are discrete on the tongue, cheeks, lips, and often confluent along the gum margins. There is at times a foul odor, especially in the neglected cases. The patient has great pain on eating and often refuses all food. Enlargement and tenderness of the lymph nodes under the jaw cause pain on movement of the neck. After a few days, the patient is the picture of utter misery. He drools constantly, refuses food, and cries even on

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From the Department of Pediatrics, New York University, and The Children's Medical Service, Bellevue Hospital.

taking water into the mouth. The gums are often the main site, and they may become greatly swollen and ulcerated along the free margins, with only a few ulcers on the tongue, cheeks, and lips. Sometimes the discrete ulcers dominate the picture, and the gingivitis is minimal. Many writers call this form "aphthous stomatitis," a poor term. (Others use "aphthous" for canker sores, and Stedman's *Dictionary* uses the term for thrush.) We believe it is all one disease, a gingivostomatitis. The duration is from ten days to three or four weeks, although most cases are over in less than fourteen days. Brenneman[2] says, "The disease is over in three to four days." The duration is never so short in New York, where it lasts about two weeks under old forms of treatment. Black found an average duration of eleven days.

Gingivostomatitis has been, and by some writers still is, attributed to the Plaut-Vincent's organisms, but it is probable that the association is accidental. It is certainly inconstant. Dodd, Johnston, and Buddingh[3] have found that the herpes virus can be recovered from the lesions. Unfortunately, for simplification of the terminology, they have called the disease "herpetic stomatitis," a term which has often been used for the canker sore. From a purely clinical standpoint, canker sores resemble herpes simplex more than does gingivostomatitis. Furthermore, there is no immunity to herpes, in many persons at least. There may be an immunity developed in gingivostomatitis, although it is not a common enough disease to make it likely that a child would have it more than once. We feel it would be wise to await further investigation before transferring old terms and increasing the present confusion. Gingivostomatitis has little resemblance to the clinical course of herpes simplex. It runs through families and armies and is communicable by contact or the use of common dishes or utensils. There is a seasonal peak of cases in the fall months. There is a definite febrile period preceding the local lesion, and second attacks are not described. Further study seems necessary to clarify its relation to herpes and to common canker sores. Trench mouth in armies has a course so much like gingivostomatitis of children that it must be closely related, if not identical.

Acute gingivostomatitis is fairly common in hospital and in private practice. It is an acute and extremely uncomfortable disease. There is a weight loss of several pounds in many cases. Furthermore, a child who has fever and who is able to eat little or nothing for many days is often in such a weakened condition that he may contract other infections. We have seen pneumonia more than once as a sequela. The disease is, therefore, not to be taken lightly, but should have careful treatment in the acute stage and a guarded convalescence.

The history of the treatment of this disease illustrates the old saying that, where many remedies are recommended, it is probable that most of them are worthless.

A generation ago potassium chlorate was thought to be a specific for stomatitis and is still recommended by some writers. It was used as a mouthwash and also internally, often in such large doses that kidney irritation was produced. The stomatitis ran its course.

All sorts of local treatments have been used. Many were the mouthwashes and the drugs painted on the ulcerated areas. Alum powder, silver nitrate, copper sulfate, zinc sulfate, iodine, benzoin, myrrh, argyrol, formalin, ipecac, mercurochrome, salvarsan, and other arsenic preparations, sodium perborate, and gentian violet have been most commonly used. There are doubtless others which have been tried. The last two are in style of late, but have little more effect than the others. Perhaps perborate is the best mouthwash, although there is no startling improvement from it. To those who believe that the Vincent's anaerobes are responsible, oxidizing agents seem necessary. We have never seen the slightest effect from gentian violet except the staining of the child's face and most of his environment. Dobell's solution held in the mouth, full strength, gives some relief, because of the local anesthetic action of the phenol it contains.

Intravenous salvarsan has been given many times under the assumption that stomatitis is due to the Vincent's symbiosis. Faber[4] and others have thought that it shortened the disease. In our experience it has helped no case. Black[1] shows that the disease is probably not due to Vincent's organisms, as we have believed for a long time, and that there is no improvement after arsenical preparations. It seems quite unjustifiable to give a drug like salvarsan, which is a potential poison, unless there is real evidence that it does some good.

Cevitamic acid has been given for acute stomatitis, with the idea that there may be a scorbutic factor in the etiology. There is little reason to suspect this, since the disease affects children on a normal diet, acts like an acute infection, and is contagious from one child to another. We have seen whole families contract it and physicians acquire it from patients. Cevitamic acid has made no difference in the cases in which we have seen it tried. Nicotinic acid also has been used, with no appreciable effect. Gerstenberger[5] believed that remarkable results were obtained from the use of vitamin B. The durations of the cases were not notably less than the average.

The paper by Black[1] describes the clinical course admirably. But there is a note of despair in it when the treatment is discussed. He states, "There is no established specific treatment for the disease." He recommends a nonirritating soapy dentifrice, merely for cleanliness of the mouth, and says, "Caustics are dangerous when applied to the inflamed gums. They may cause destruction of tissue, with subsequent retraction of the gums."

Brennemann[2] advises no local treatment since the disease is self-limiting.

Griffith and Mitchell[6] suggest permanganate, silver nitrate, boric acid and myrrh, burnt alum, perborate, potassium chlorate, and gentian violet.

Holt and McIntosh[7] advise oxidizing agents, such as peroxide or perborate.

Zemsky,[8] in *Oral Diseases*, recommends tincture of iodine or silver nitrate. (Anyone who has had either of these applied to a canker sore in his own mouth, with the resulting severe pain, will never order it for a child.)

Merritt,[9] a prominent dentist and specialist on disease of the gums, believes gingivostomatitis due to Vincent's organisms. For twenty-five years he has used the following plan:

1. All necrotic material is carefully cleaned away.
2. Chromic acid, 5 per cent, is applied on cotton, bathing all the gums and teeth and the spaces between them.
3. Mouthwash of peroxide with weak bichloride of mercury or potassium permanganate is used between treatments.

He advises treatment daily, three to six times in all. Arsenical treatment is condemned.

Ganley,[10] in 1920, reported the results of various remedies for trench mouth in the army and advocated chromic acid (7 per cent) as the most useful remedy.

Prinz and Greenbaum,[12] in their text on *Diseases of the Mouth*, note that trench mouth was present in Xenophon's army (401 B.C.) and that Napoleon's armies were decimated with it. They state that from 10 to 20 per cent of the soldiers in the World War suffered from the disease. They recommend cleansing and application of 5 per cent to 10 per cent chromic acid, "which acts as a veritable panacea." They consider potassium chlorate and arsenicals worthless.

Cobe and Grace,[11] who are dentists, recommend chromic acid and condemn arsenicals.

Rosenthal[13] states that chromic acid seems to be the most popular treatment for "Vincent's infection" and that it has been used since 1870. Its dental advocates have ascribed its effects to its oxidizing properties (since the Vincent organisms are anaerobic), but under the conditions of actual use no oxygen is liberated. Rosenthal found that 8 per cent chromic acid did not kill spirochetes. He believes that its action is purely caustic and advises against its use. He also found that perborate had no more effect on motility of spirochetes than tap water.

It is noteworthy that most dental authorities recommend chromic acid and that this recommendation does not appear in pediatric literature or texts.

The United States Dispensatory states that chromium trioxide is a coagulant of albumen and, therefore, an astringent and an active germicide, killing anthrax bacilli in 1 per cent solution. It is only an oxidizing

agent in concentrated solutions. Some of the dentists who believe the Vincent's organisms to be the cause stress the oxidizing effect of the drug. This is an obvious fallacy.

About twenty years ago a dentist, Dr. S. Welling Van Saun of New York, called the attention of one of us to the value of chromic acid as a local treatment for a gingivostomatitis. The prompt improvement following its use on private patients and in the hospital was convincing, and it has been used routinely ever since.

The technique of the use of chromic acid solution is important. Van Saun's original suggestion was to wash the mouth with potassium permanganate solution or hydrogen peroxide, dry the areas to be treated, apply the chromic acid (7 per cent aqueous solution), and follow by painting with tincture of myrrh. The latter, being an alcoholic solution, is painful and makes the child object strongly, so we have omitted it. The technique we have used is as follows:

1. The patient rinses the mouth with a mouthwash if he is old enough to do so. If there is much accumulation of sordes or sloughing material on the ulcerated areas, a weak peroxide solution is used, followed by a mouthwash. The dentists insist that a thorough cleansing is important. The kind of mouthwash used is unimportant. It is often advisable to let the child have one to which he is accustomed and the taste of which he likes. Dobell's solution, plain or diluted one-half, or perborate of soda solution is perhaps the best.

2. Several swabs of cotton *tightly* wound on wood applicators are prepared. These swabs should be about the diameter of a lead pencil and 1½ inches long. The gums and ulcers are dried carefully with a swab. Then another swab is dipped into the chromic acid solution (5 per cent to 7 per cent in water) and applied directly to the ulcers and the inflamed edges of the gums. The swab must be wet, but not dripping. Some of the solution is gently worked in between the gums and the teeth. It is best to dry and treat a small area at a time, not more than from one-half to one-third of the dental arch at once. This means dividing the total gum area into from eight to twelve parts, upper and lower, inside and outside of the teeth. This treatment is repeated twice a day for from one to three days, then once a day.

3. Between treatments the patient can use a mouthwash.

4. The general treatment is that of any febrile illness. Bed rest is necessary until the child is well and back on a full diet, not merely during the febrile stage. Especial attention to the bowels is needed, since the food intake is so low. A laxative at night saves the morning struggle over the enema. The diet should be one which will not cause pain, i.e., nothing salty, sour, spiced, too sweet, or too hot. Milk toast, cereal gruels, and creamed soups are bland foods for the febrile stage. More milk or junket may be added as soon as the fever leaves, and then a gradual return is made to a full diet as the gums improve.

The results of this plan of treatment are quite satisfactory. In the first place, the chromic acid has a definite analgesic effect. The application causes little or no pain, although young children object to all treatments, of course. Patients can eat with more comfort for several hours after a treatment. This fact alone justifies the plan.

The inflammation of the gums begins to improve after two or three treatments, and in from forty-eight to seventy-two hours there is a distinct change. One cannot expect the ulcers nor the ulcerated gum edges to be healed at once. The replacement of necrotic tissue takes time, and the swelling and congestion also subsides gradually, so that the disease lasts several days after the treatment is started, if one measures complete cure by the disappearance of all congestion of the gums. But the test of the treatment is that improvement begins as soon as it is started, and the impression that the patient is much more comfortable in a day or two is shared by all who have watched patients treated in this way. Older children and adults say that there is no question about the relief to the discomfort of eating. We have never seen any indication of gum atrophy from the use of the acid nor any scars of ulcers. Several patients treated years ago by this method have been re-examined and found to have normal gums. The slough which is formed by the acid is extremely superficial, and it is probably merely the coagulation of already necrotic material present on the surface of ulcerated areas.

The results in hospital cases may be less striking and prompt than those in private practice. Private patients are more likely to be treated early and thoroughly, while hospital cases are neglected and come in only after a week or more of progressive inflammation. In addition, the technique plays a most important part in the success of the treatment. A new member of the house staff may merely make a gesture at it, especially if the child struggles violently. Each new house officer must be trained for each new case. Naturally, the results will be less good than in cases where the treatment is well done by one with experience. The treatment should not be entrusted to a nurse unless she has been carefully instructed and supervised.

The records of the Children's Medical Service at Bellevue Hospital show about twenty cases a year. Sixty-eight of the old cases which had the best records were selected for analysis. Boys and girls were equally affected. The age distribution shows that most of the cases occurred between the ages of 1 and 3 years, with the greatest number at about 2 years and the range from 1 to 10. Of the sixty-eight cases, thirty-six were treated with chromic acid (although some were obviously insufficiently treated), and thirty-two had other methods used, mostly perborate or gentian violet.

The total duration of the disease is roughly the same in both groups, about thirteen days. But the duration of the disease after starting

chromic acid treatment averages about two days less than the duration in patients treated otherwise (about 7½ and 9½ days, respectively, to complete healing). This does not give a true idea of the relief given by chromic acid, nor of the general impression that improvement begins more promptly with its use than with other remedies.

Since this paper was read, twelve cases of gingivostomatitis have been under our care. The treatment has been more systematic perhaps, and careful notes have been kept. Six of these patients had symptoms from one to two days before treatment. They were improved in from twenty-four to forty-eight hours and practically well in about four days. The total duration of the disease ranged from five to ten days, with an average of eight days from onset to completely normal gums and mouth. The other six cases had lasted from three to seven days before treatment. They improved promptly and were all noted to be much better in about four days. They were completely normal in from five to ten days, with an average of less than eight days after treatment. The total duration was from eleven to seventeen days, with an average of thirteen days. It seemed obvious that the chromic acid treatment relieved the acute symptoms and caused a marked improvement in about four days after treatment was begun, no matter how long the disease had existed. The time necessary for a complete return to normal depends upon the duration of the disease before the treatment is started. The neglected cases have more ulceration and swelling, and it inevitably requires a longer time for complete resolution. The prompt improvement and relief of pain on eating was noteworthy in all these children.

In several private patients in whom the treatment was begun at once as soon as the gum margins became red and isolated ulcers appeared, the course was very short, and the mouth healed in three or four days.

The following cases may be cited:

1. A child of three had been under the care of a physician for about four weeks for acute stomatitis. The physician had ordered the usual applications, mainly perborate and gentian violet, with no results. The child was much debilitated, a picture of abject misery; saliva drooled from the mouth constantly, and he would eat little and suffered great discomfort. The gums were extremely swollen, nearly covering the teeth, and ulcerated at the margins, and the tongue and cheeks still showed many ulcers.

Treatment with chromic acid solution gave prompt results. In thirty-six hours improvement began, and in three days the whole mouth was healing.

2. An adolescent girl was seen during the summer outside the city. She had had a sore mouth for about one week. Her physician had given two intravenous doses of salvarsan and ordered it applied

locally, as well as in a mouthwash. She had grown steadily worse. The gums were extremely inflamed, and there were many ulcers in the mouth.

After chromic acid was applied, she could eat at once with comfort. Her mouth was treated twice a day for two days, and once a day for two more. She began to improve at once and was practically well on the third day.

3. A resident on the Children's Medical Service at Bellevue Hospital had a severe attack while on his vacation recently. He had two or three days of fever and severe muscular aching before the sore mouth began. When the gingivitis appeared, he treated himself with chromic acid and obtained the greatest relief, being able to eat with comfort after each application.

The ordinary canker sore is usually treated by the dentists by applying 95 per cent phenol or trichloracetic acid. We have found 7 per cent chromic acid just as effectual in anesthetizing these lesions which are sometimes very painful. It seems to accelerate healing. Silver nitrate is very painful and is of no value in our experience.

SUMMARY

Chromium trioxide (5 to 7 per cent solution) is the only local application which has given us the slightest effect in treating gingivostomatitis. If the solution is used with the proper technique, improvement begins promptly, and the disease is definitely shortened, especially in the cases in which treatment is begun early. The relief from pain on eating which follows a treatment is enough to justify its use. There is no danger of a caustic effect nor of gum atrophy.

This solution is also useful in relieving the pain and shortening the duration of the common canker sore.

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DISTURBANCE OF OSSEOUS AND LIPID METABOLISM IN A CHILD WITH PRIMARY CARCINOMA OF THE LIVER

ARILD E. HANSEN, M.D., MILDRED R. ZIEGLER, PH.D., AND IRVINE MCQUARRIE, M.D.
MINNEAPOLIS, MINN.

THE incidental discovery of a marked degree of lipemia and pronounced osteoporosis of the entire skeleton in a child suffering from a large hepatic tumor suggested the investigation herein reported. While extensive liver damage has long been known to result in a disturbance of the lipid economy, a survey of the literature reveals but few references to any relationship between hepatic function and osseous metabolism. Whipple[1] found that dogs with bile fistula developed abnormalities of the bones associated with a loss of inorganic constituents. The skeletal deformities of these animals were prevented by adding cooked liver to the diet. The presence of an abundance of bile pigment and the absence of an excess of fat in the stools of our patient made it unlikely that the osteoporosis could be explained on the basis of vitamin D deficiency resulting from impaired absorption of this substance.

The present study was undertaken primarily to determine the nature and the degree of impairment of liver function in the subject referred to above and to investigate the possible relationship between this disturbance and the obvious failure of the bones to retain calcium and phosphorus. In addition, special attempts were made to correlate alterations in the plasma lipids with the disturbance in hepatic function and also to determine the effects of the prolonged lipemia per se upon the various fixed tissues, including the bones. These objectives required, in addition to frequent clinical examinations, repeated x-rays of the bones and determinations of the lipids, inorganic phosphorus, calcium, and serum proteins at various intervals over a considerable period of time. Calcium and phosphorus balances were measured under various conditions when the diet was approximately normal and again when it was high in these constituents. These special studies and certain functional and diagnostic tests also performed will be described below.

To facilitate an understanding of the bizarre and unusual manifestations of this case, the clinical and routine laboratory data are presented in some detail.

CLINICAL DATA

A 10-year-old boy was admitted to the University of Minnesota Hospitals on Sept. 20, 1935, with the complaint of pain in the back and a peculiar gait of seven months' duration.

From the Department of Pediatrics, University of Minnesota.
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Present History.—In March, 1935, while playing, the child slipped and fell, assuming a sitting position, and was then suddenly jumped upon by a fellow playmate. He immediately complained of a sharp pain in the region of the lower thoracic vertebrae, which radiated to the right side. The pain continued for about three weeks, but was not sufficiently severe to prevent his going to school. The child then seemed quite normal until May, when he again began to complain of severe backache which made it impossible for him to stoop over. Because of the accentuation of the pain, which again began to radiate to the right side of the chest, he was sent to the local hospital for study. About this time the mother had noted a slight bulge in the region of the lower ribs on the right side of the chest.

A letter obtained from the referring physician (Dr. J. F. Norman of Crookston, Minn.) disclosed a history similar to that obtained by us. His examination at that time revealed "the presence of a large mass just below and to the right of the ensiform cartilage which seemed to be a part of or connected with the liver, being somewhat firm and nodular and moving with respiration." Although the child walked holding the back very stiff, the vertebral column seemed very flexible, and there was no impairment of the movement of the lower extremities. No tenderness was elicited, and the child never suffered from night cries. The physician found that there had been tuberculous cattle on the farm some years before, but he did not believe this to be of significance. The urine examination revealed no abnormality; the hemoglobin was reported to be 87 per cent, with 4,390,000 red blood cells and 8,900 leucocytes. After nine days in the hospital, the patient seemed somewhat improved; however, soon after he returned home, he developed marked weakness and difficulty in walking. His lack of strength was so marked it was necessary for him to support his legs with his hands, even while standing. The abdominal mass became more distinct, and when the child was examined by his physician in August, the latter was convinced that the large nodules so easily palpable were contiguous with the liver. An x-ray examination of the lower spine was made at that time, but no abnormality of the osseous tissue was reported. The findings in these films will be discussed later. The patient developed some anorexia and noticeable weight loss, and finally was sent to the University Hospital for further study.

Past History.—The child always had been in good health. The natal, developmental, and feeding history revealed no significant data. He had scarlet fever at 2 years of age and measles six months later. Occasionally he complained of right temporal headaches, and at times, of slight dyspnea on exertion, which seemed especially marked just before the development of the present illness. At no time were jaundice, edema, or abnormal stools noted.

Family History.—The father died at the age of 49 years from a so-called "spinal trouble" following an injury. The mother was living and well and was dependent upon a small widow's pension for support. There were nine other children in the family, all living and well. There was no tendency to cancer in the family and no known exposure to tuberculous persons.

Physical Examination.—On admission to the hospital the boy presented a rather striking picture because of a slightly dwarfed figure with a definite foreshortening of the thoracic cage with minimal kyphotic and pigeon-breast deformities, together with a visible protrusion of the epigastrium and lower chest wall (Fig. 1). For a boy of 9 or 10 years he was rather slight of stature, visibly weak, and frail in appearance, and these features were accentuated by a very shy disposition. He was not in pain and did not seem to be distressed at the time of the examination. Over the shoulders, forearms, and back, a rather marked growth of hair, soft and of fine texture, was noted. His height was 48 inches (122 cm.), and his weight, 51 pounds (23.2 kg.). No abnormalities were noted in the pulse, respiration, and blood pressure. Most significant were the findings in the abdomen. A markedly

protruding mass, which on palpation was firm and nodular, was present in the epigastrium. This moved with respiration, but did not pulsate. The mass extended from the costal margin on the right side to 3 inches (7.6 cm.) below the xyphoid process and seemed to be associated intimately with the liver. There were no tenderness and no areas of softening in the mass. Other physical findings were of no particular moment as regards the problems involved in this case.

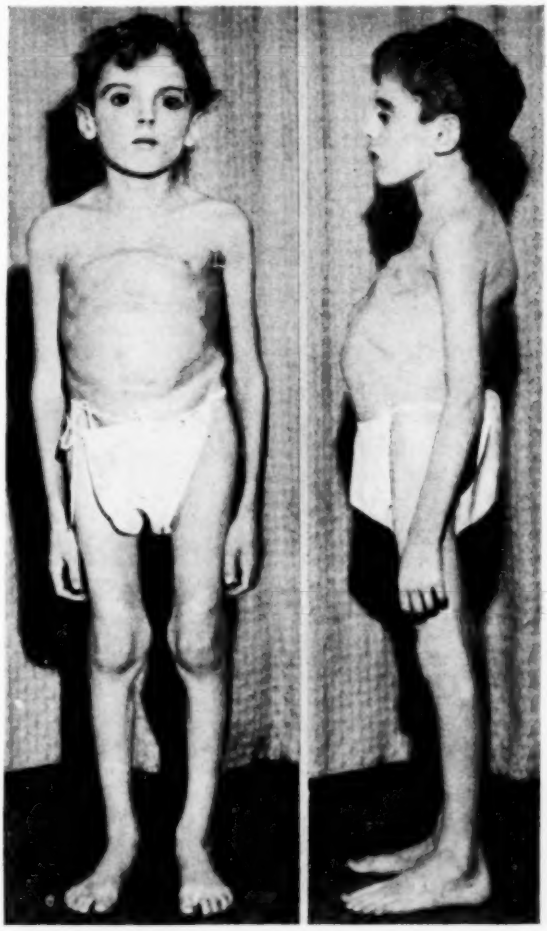
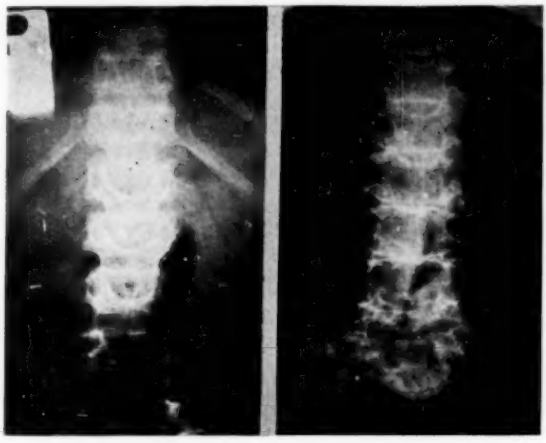


Fig. 1.—Case 1, L. C. Ten-year-old boy with dwarfed appearance and various deformities of the spine and thorax, as well as protruding mass in the epigastrium.

Laboratory Examination.—Routine laboratory examinations revealed the following: hemoglobin, 81 per cent; erythrocytes, 4,170,000; leucocytes, 9,800, with 60 per cent neutrophiles and 40 per cent lymphocytes. The urine showed no reaction to the tests for albumin and sugar and no evidence of Bence-Jones protein. The Wassermann and Mantoux reactions were negative, and the Schick, positive. The

inorganic phosphorus of the serum was 5.6 mg., and the serum calcium 11.6 mg., per 100 c.c. It was not possible to determine the icteric index because of the marked cloudiness (lipemia) of the serum.

X-Ray Examination.—The remarkable degree of osteoporosis of the skeletal framework was so striking as to compel detailed study of the entire osseous system. Most noteworthy was the extreme resorption of the bodies of the vertebrae, causing them to be definitely flattened. The distortion of the vertebrae was so marked and the intervertebral areas so expanded that it was difficult to obtain a clear visualization of the spine, the appearance suggesting an exact reversal of the actual condition (Fig. 2). The rapidly progressive nature of the disturbance was recognized when the films of the spine were compared with those taken two months previously at the local hospital (Fig. 2). The bones of the skeleton showed a marked degree of



a. *b.*

Fig. 2.—X-rays of spine taken (*a*) at local hospital three months prior to admission and (*b*) after admission to the University Hospital.

decalcification, and, in addition, the pelvis and femora showed a marked coarsening of the trabeculae. The lung fields were clear, and a flat plate of the abdomen revealed the presence of a large mass on the right side, apparently associated with the liver. The presence of such a marked degree of osteoporosis suggested the possibility that osteogenesis imperfecta, hyperparathyroidism, or a diffuse infiltration from some type of tumor might be responsible for the findings encountered. The appearance of the femora and pelvis suggested somewhat the leucemic type of infiltration. Since the intravenous pyelogram showed a downward displacement of the right kidney, the possibility of a tumor of the adrenal cortex or a neuroblastoma of the genital ridge was considered.

Diagnosis.—The diagnostic impression was that of a tumor of the abdomen, most likely the liver, either primary or metastatic, with the additional possibility of a primary tumor in the right suprarenal gland. It was not possible to explain the extreme degree of decalcification of the skeleton. An exploratory laparotomy was elected, which was performed under cyclopropane anesthesia on Oct. 11, 1935.

Operative Findings.—The liver was found to be enlarged, and both lobes were studded with many rather thick firm nodules about the size of small walnuts. The liver tissue was very vascular and bled rather freely when an attempt was made to aspirate one of the nodules. The surgeon, therefore, deemed it inadvisable to remove

a piece of the tissue for biopsy. The aspirated material, which had the appearance of a blood clot, was sent to the laboratory for study.

Pathologic Report on Biopsy Specimen.—Microscopic examination revealed a remarkable amount of tissue in the specimen. The sediment contained large shreds and blocks of epithelial cells which were characterized by an abundant amount of cytoplasm and were almost completely vacuolated. The cell membrane was intact, and the nucleus was small, round, and dense. No mitotic figures were seen, and no sinus spaces were present between the cords of these cells (Fig. 3.) The pathologist

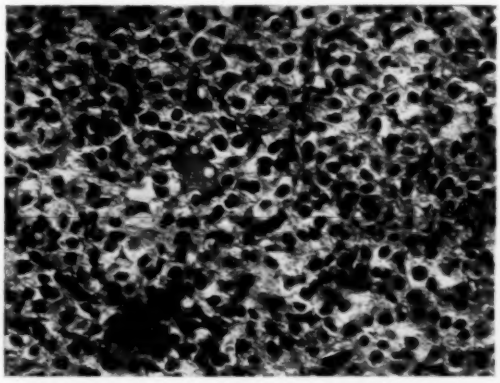


Fig. 3.—Photomicrograph of tissue obtained by aspiration of vascular tumor in the liver.

offered the following interpretations: "The cells have an arrangement of a striking resemblance to liver cells in which the usual sinus spaces between the cords are absent. The alternative type of tissue which may give this appearance is the lining of an hemangiomatous cyst which is proliferating and giving rise to endothelial masses. More remote possibilities are hypernephromas or metastatic tumor from the adrenal cortex. If the cells represent liver cells, they must arise from very disorderly growths in which the usual formation of normal cords with alternating liver sinuses is absent. The final diagnosis depends a great deal upon the gross appearance of the lesions at the time of operation." One pathologist who was interested in the embryologic development and the histology of the parathyroid glands was particularly impressed by the remarkable similarity of this tissue to that of the parathyroid gland.

Subsequent Course of Events.—In order to determine the extent of destruction to the liver, thorotrast was administered intravenously. The x-ray revealed one very large, sharply defined, rounded defect characteristic of a primary tumor, as well as some smaller areas of rarefaction which suggested a more diffuse condition, such as metastatic tumor masses. As a palliative measure it was decided to use deep x-ray therapy, which was then given in a series of seven exposures. Because of the unusual nature of the condition, it was decided to allow the patient to recuperate from the operation and later to return to the hospital for more complete metabolic studies. He was sent home on Nov. 8, 1935, at which time he weighed 42 pounds (19.1 kg.) and was readmitted on Feb. 25, 1936, for further deep x-ray therapy. Some improvement in his general condition had occurred, although he was still not very active and had a rather poor appetite. The mass in the abdomen seemed to be much firmer and possibly somewhat smaller. He weighed 52.6 pounds (23.9 kg.) at the time of his discharge from the hospital on March 12. The patient was readmitted

to the hospital for the third time on May 19, for the express purpose of conducting further metabolic studies. He felt quite well, although he did complain of slight dyspnea on exertion, of some anorexia, and of tiring rather easily at times. The abdominal mass had decreased somewhat further in size. His weight had decreased to 48 pounds (21.8 kg.), and his height was 47 inches (119.5 cm.). The special studies of the mineral metabolism and lipid metabolism, as well as further liver function studies, were performed at this time and are recorded in a subsequent part of this paper. In all, the patient was in the hospital for a period of 208 days, during which time there was a definite gradual decrease in weight and a decline of 1 inch in stature. He was usually quite active, and his appetite was fairly good most of the time. Only very occasionally did he complain of pain. In fact, he was very comfortable practically all the time and seemed to be quite oblivious to the subjective sensations, especially to cold. Even though the atmosphere was rather chilly at times, he preferred to go without a shirt, being content with a thin pair of trousers as his entire wardrobe. X-ray examinations of the entire skeleton disclosed no great change from the previous appearance of the osseous system. He was discharged from the hospital on Dec. 13, 1936, at which time he weighed 44 pounds (19.6 kg.). The subject was again admitted on Jan. 11, 1937, because of increasing pallor and vomiting. There was marked wasting of the extremities, and a mild icterus was noted for the first time. The tumor had become huge, extending down to the crest of the right ilium. He had undergone still further shrinking in height, being but 46 inches (117 cm.) tall, a decrease of 2.8 inches (7 cm.) since his first admission to the hospital eighteen months before. Roentgenologic examination of the skeletal structure revealed an even more extreme degree of decalcification. Multiple metastases were seen in both lung fields, and thorotrast was still present in the liver. Numerous fractures of the ribs were seen. At no time did the stools appear acholic or fatty in nature. No abnormality of the urine was present. The hemoglobin had dropped to 60 per cent, with 2,960,000 red cells, and the leucocytes numbered 9,000 with 83 per cent neutrophiles, 16 per cent lymphocytes, and 1 per cent eosinophiles. The patient gradually became worse and died Feb. 5, 1937.

Autopsy.—The report of the autopsy performed by Dr. A. A. Nelson is limited to only the pertinent positive findings.

Gross Findings.—The *peritoneal cavity* was found to contain about 0.5 liter of free blood, which appeared to come from a fragmented and hemorrhagic portion of tumor tissue in the liver. Each *lung* weighed 140 Gm., and the pleural surfaces were studded with single and conglomerate nodular tumor metastases. There were perhaps from fifty to one hundred nodules in each lung, groups of nodules measuring up to 1 cm. in diameter and most of them subpleural. The tumor nodules were whitish in color. There was no pneumonic consolidation. The *spleen* weighed 245 Gm., was soft, homogenous, pale red, and contained a single, soft, reddish-white tumor metastasis measuring 2.5 by 2.5 by 3.5 cm. The *liver* was markedly enlarged, filling the upper two-thirds of the abdomen, and weighed 3,160 Gm. The surface of the liver was hobnailed and showed many hundreds of tumor nodules. On section (Fig. 4), little hepatic tissue could be seen, the whitish tumor nodules being very numerous, especially in the right lobe. In the right lobe about half the tumor was green and the rest whitish in color, while in the left lobe, most of the tumor tissue was white. The *adrenal*, *parathyroid*, *pituitary*, and *thyroid glands* all appeared to be normal grossly. The right *kidney* weighed 45 Gm. and, on section, had a thin cortex and was fibrous in consistency. The left kidney weighed 80 Gm., was swollen, pale, and seemed to be of normal consistency. The *ribs* were thin, soft, and could be bent like cardboard. The lower ribs in their lateral portions showed about two dozen spontaneous fractures, a few being recent and showing no sign of healing and the greater number showing a moderate degree of callus formation. The *vertebral bodies* were soft and markedly atrophic. Most of the bodies were from 5 to 8 mm. in thickness

and some as thin as 2 mm. The intervertebral discs were so expanded that the total length of the vertebral column appeared to be practically normal (Fig. 5). A portion of the right femur was removed. This consisted of a shell of bone from 1.5 to 2.0 mm. in thickness, surrounding a cavity filled with red marrow and containing practically no spongy bone.

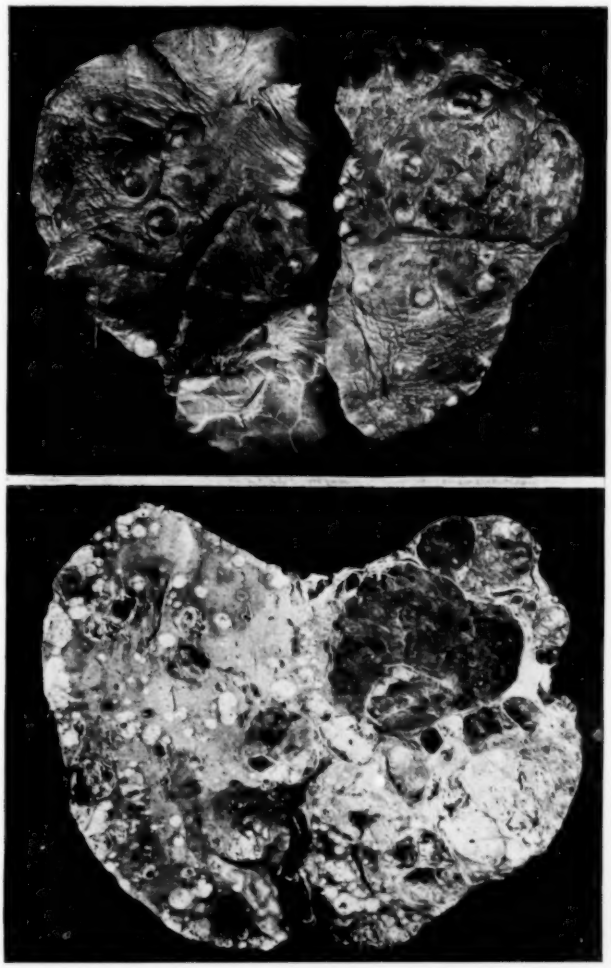


Fig. 4.—Ventral surface of the liver and cut section showing numerous tumor nodules.

Microscopic Findings: Liver.—A hepatoma type of carcinoma with many mitoses was found. There were only a small number of reticuloendothelial cells, and in the green portions of the liver tumor, there were some ductlike structures containing bile in their centers. Much thorotrast was seen in the uninvolved portions of the liver, and these areas showed moderate fatty changes. Scattered throughout the

tumor and its metastases and also in the uninvolved areas of the liver were small numbers of large lipid-laden cells similar to xanthoma cells (Fig. 6).

Spleen.—Almost the entire pulp was replaced by large lipid-filled cells similar to those of the liver (Fig. 7). There were only a few of these cells in the sinuses. Thorotrast was also visible in the spleen.

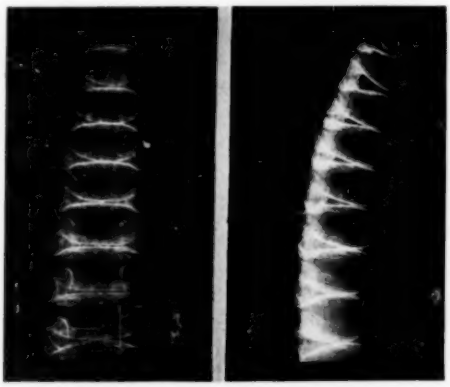


Fig. 5.—X-ray of section of spine showing the extremely flattened vertebral bodies and widened intervertebral discs.

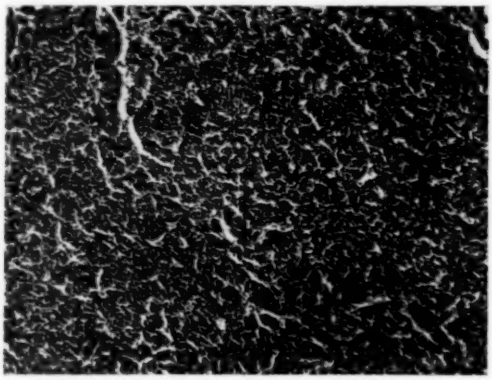


Fig. 6.—Photomicrograph of section through the liver, showing hepatoma type of tumor cells.

Lungs.—The metastases here appeared the same as in the white portions of the tumor tissue in the liver. Xanthoma-like cells were also seen.

Kidney.—The left kidney appeared normal microscopically, but the right kidney showed a slight glomerular and tubular atrophy. The glomeruli and, to a lesser extent, the tubules contained the same type of lipid-filled cells as were found in the liver and spleen. The greater portion of the glomeruli was involved, some containing only a few of these cells in the capillaries, while others contained masses of about one-half dozen cells, causing the capillary loop to be distended.

Bone Marrow.—This contained the same type of xanthoma-like cells as found elsewhere (Fig. 8). Fat stains and special study of the spleen by a sudan stain showed

that it contained large quantities of intercellular fat, nearly all being in the pulp. Apparently there was so much fat present that some was extracellular, lying free in the pulp, also filling the trabeculae and surrounding the lymphatic follicles. There were some fat-filled macrophages in the sinuses. The Nile blue sulfate stain suggested to the pathologist that this fat was not neutral fat, and the condition could be correlated with the marked cholesterosis present.

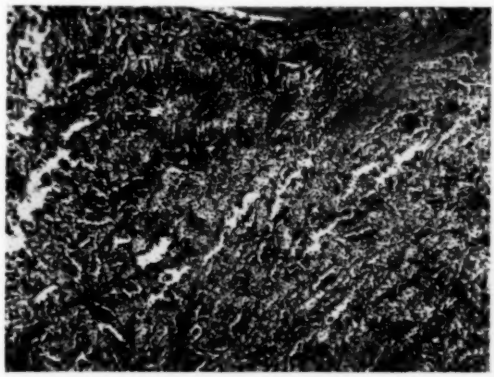


Fig. 7.—Photomicrograph of section through the spleen, showing the large number of lipid-laden cells and some areas with thorotrast deposits.

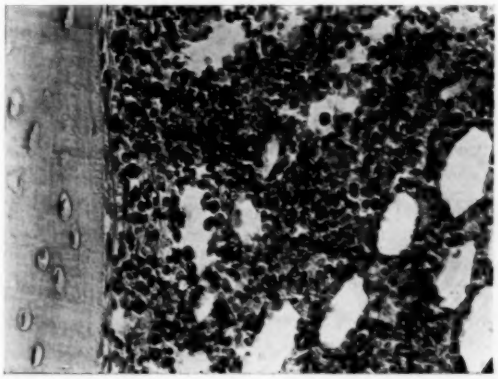


Fig. 8.—Photomicrograph of bone marrow, showing the same types of fat-filled cells as seen in the spleen.

Diagnosis.—The final diagnosis was: (1) Primary carcinoma of the liver (hepatoma type), with metastases in the lungs and spleen; (2) intraperitoneal hemorrhage from ruptured carcinomatous area of the liver; (3) lipid histiocytosis of the spleen, liver, lungs, right kidney, and bone marrow; and (4) extreme atrophy of bones, with spontaneous fractures of the ribs.

SPECIAL DIAGNOSTIC STUDIES

This case seemed to offer an unusual opportunity to study various functions of the liver in order, first, to determine their significance from

a diagnostic viewpoint, and second, to follow the sequence of failure of the liver as regards its various functions. To expedite the presentation of these data, they will be presented in outline form, but no attempt is made here to suggest any relative importance of the various tests to hepatic function.

Carbohydrate Tolerance.—After the administration of 40 Gm. of glucose, the following blood sugar curve was obtained: fasting, 84; one-half hour, 157; 1 hour, 170; one and one-half hours, 155; two hours, 170; and three hours, 78 mg. per 100 c.c. whole blood. This suggested some evidence of impaired glucose tolerance. Fasting blood sugar determinations on two other occasions were 47 and 77 mg. per 100 c.c. blood. The galactose tolerance test was reported as being negative.

Thorotrast.—Thorotrast was given early in the course of study in order to determine the extent of liver destruction, which was found to be extensive.

Bromsulphalein Test.—The bromsulphalein dye test of Rosenthal showed the excretion of the dye to be 25 per cent, whereas the upper limit of normal was expected to be no more than 10 per cent. This was another definite evidence of impaired liver function which was demonstrable fairly early in the course of the disease.

Bile Pigment Function.—The urobilinogen excretion was 0.45 mg. per day, a value which is essentially normal. The stercobilin tolerance test revealed an urinary output of 13.6 mg. in twenty-four hours following the administration of 50 mg. of stercobilin intravenously. We are indebted to Dr. C. J. Watson and his co-workers for performing these tests. Insufficient data have been obtained from normal children to make a strictly just comparison of these findings, but judged by adult standards, it would appear that the amount of stercobilin retained by this subject was much less than that retained by any one of the normal adult subjects studied.

Serum Proteins.—The importance of the liver in the genesis of serum proteins is well recognized. The determinations of the serum proteins, with the albumin and globulin fractions made at various intervals in this study, are summarized in Table I. Despite the fact that there was a great destruction of hepatic tissue, the serum proteins maintained themselves at essentially normal levels. It was only late in the disease, almost

TABLE I

VALUES FOR TOTAL PROTEINS AND ALBUMIN AND GLOBULIN FRACTIONS OF THE SERUM AT VARIOUS INTERVALS THROUGHOUT THE STUDY

DATE	DIET	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	NONPROTEIN NITROGEN (MG. %)
5/21/36	General	7.89	5.26	2.63	40.2
10/26/36	Special	7.41	3.53	3.88	44.4
1/14/37	Special	8.37	–	–	41.4
2/ 5/37	General	5.16	3.88	1.28	29.4

terminally, that the levels of the total proteins dropped, and this could well be explained on a nutritional basis. It thus appeared that, even though but little hepatic tissue was present, it was effectively able to preserve the normal values for the serum proteins.

Bence-Jones Protein.—Repeated examinations showed the urine to be negative for Bence-Jones protein.

Hematopoiesis.—At no time was any evidence of a disturbance of the hematopoietic system demonstrated. The roentgenologists had stated that the changes in the bones of the pelvis and femora were compatible with leucemic infiltrations. Therefore, repeated studies of the morphology of the blood were made. The hematologist was never able to demonstrate any abnormality of either the red cell or white cell series. It was only late in the course of the illness that the hemoglobin dropped to 61 per cent, after maintaining itself at the 80 per cent level most of the time.

Phosphatase Activity.—The serum phosphatase activity was disclosed to be 4.23 Bodansky units, a value which is considered to be normal. It is well known that certain types of liver disease may be associated with changes in the phosphatase activity of the serum. The normal value obtained here also aided in ruling out hyperfunction of the parathyroid glands as a possible cause of the marked osteoporosis.

Test for Hyperparathyroidism.—Although the first attempt to determine parathormone in the blood after the manner described by Hamilton and Highman[2] suggested that a slight excess of this hormone existed in the blood of this subject, a repeat determination shortly after was definitely negative. Even though certain features of the x-ray findings were compatible with the appearance of hyperparathyroidism, no other evidence of there being a disturbance in the function of this gland was obtained, other than the suggestive similarity of the biopsy specimen to parathyroid tissue, as was pointed out by one of the pathologists. The absence of somnolence, pain in the bones, kidney stones, metastatic calcification, and other clinical findings, together with essentially normal values for the serum calcium and inorganic phosphorus, as well as the urinary output of these elements, substantiate the impression that there was no evidence of hyperparathyroidism in this case.

SPECIAL STUDY OF THE LIPID AND OSSEOUS METABOLISM

The plan of study as regards environmental conditions, collection of specimens, and chemical methods was the same as that usually used in the Metabolic Ward of the Department of Pediatrics of the University of Minnesota and reported elsewhere.[3, 4] The special diet was composed of powdered milk (klim), 90 Gm., egg yolk, 33 Gm., egg white, 30 Gm., lemon juice, 24 Gm., sugar, 90 Gm., 35 per cent cream, 48 Gm., and sodium chloride. In addition, oleum percomorphum and powdered brewers' yeast were given as vitamin supplements. Carmine and char-

coal were used as markers for the stool specimens. Collection of the urine and stool specimens was not begun until the subject had had at least two weeks to become adjusted to the diet. The length of the experimental periods varied somewhat, but it was never less than three days. All blood specimens were taken after a fast of from fourteen to fifteen hours.

In the study of lipid metabolism, the special diet was used for the most part; however, some of the blood lipid determinations later in the course of the study were made when the subject was on a general diet. This was true during the latter part of the study when the patient's condition was becoming serious and he was not able to eat well. Bile salts in the form of glycotauro, 0.6 Gm. (six tablets), were given daily for a period of twelve days in order to observe the effect upon the serum lipids. To determine further the possible effect of pancreatic enzymes and especially of the so-called fat-burning hormone "lipocaic," raw pancreas, finely ground and mixed with grape juice, was given for a period of seven days. Bloor's[5] methods were used for the determination of the lecithin, cholesterol, and cholesterol esters, and the total fatty acids and their iodine numbers were determined by the method of Wilson and Hansen.[6]

As regards the studies of the calcium and phosphorus metabolism, the special diet was calculated to allow adequate amounts for ideal retention of these elements. The average daily intake of calcium was 0.907 Gm., or 51 mg. per kilogram of body weight per day, while the daily intake of inorganic phosphorus was 0.866 Gm., or 47 mg. per kilogram per day, giving a Ca:P ratio equal to 1.09. After a control period of about three weeks, dibasic calcium phosphate, 4 Gm. daily, an amount sufficient practically to double the intake of both calcium and phosphorus, was given for a period of eight days. After another control interval, mineral studies were made during the administration of bile salts given as described above. The purpose of this procedure was to determine whether or not the marked osteoporosis could be due to the failure of the absorption of calcium because of the possible presence of insoluble soaps formed by excessive amounts of unabsorbed fat in the intestinal tract. The stool and urine calcium was determined by the method of Tisdall and Kramer[7] and the phosphorus by the method of Fiske and Subbarow.[8] The serum calcium and inorganic phosphorus determinations were made at various intervals throughout the study by the methods of Clark and Collip[9] and Kuttner and Lichtenstein,[10] respectively.

RESULTS

The findings as regards the serum lipids are summarized in Fig. 9. The results of the mineral balance studies are presented in Fig. 10, and the serum calcium and inorganic phosphorus findings are summarized in Table II.

COMMENT

Serum Lipid Studies.—The presence of a marked lipemia was observed quite early in the course of the disease. All fractions of the serum lipids seemed to partake in this increase of blood fat, in that even though the lecithin and cholesterol values were high, the calculated values for the neutral fat fraction of the serum appeared to comprise about two-thirds of the total fatty acids (Fig. 9). The relatively low values for the iodine numbers of the total fatty acid most probably are accounted for by the large amount of neutral fat in the blood. The total cholesterol levels were from two to three times the normal level, the free cholesterol being

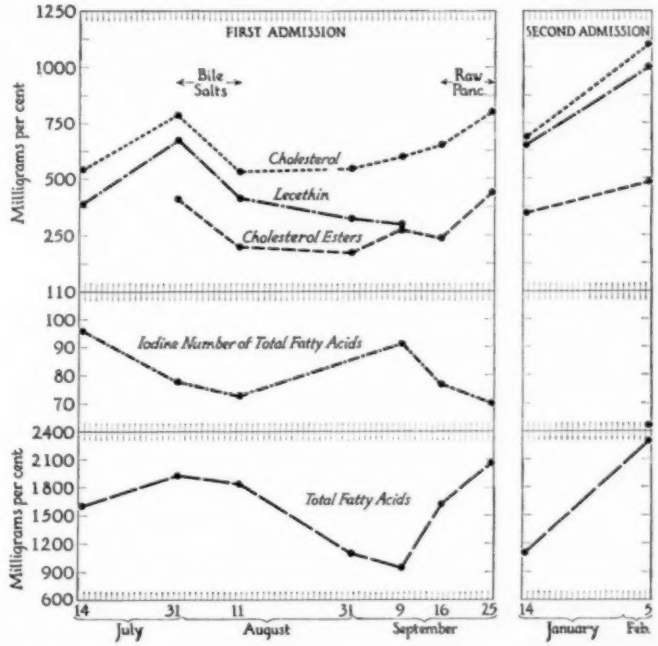


Fig. 9.—Values for the lecithin, total cholesterol, cholesterol esters, total fatty acids, and the iodine numbers of the total fatty acids of the serum during the administration of bile salts and raw pancreas, as well as at other intervals throughout the study.

particularly increased. The cholesterol ester levels, even though the cholesterol esters increased in actual amount, were relatively low, a condition which is quite typical for liver disease. The lipemia remained throughout the course of the study, and in the terminal stage of the disease, all fractions rose to abnormally high values, the total cholesterol increasing to 1,100 mg., the lecithin to 1,000 mg., and the total fatty acids to 2,200 mg. per 100 c.c. serum. A decrease in the lecithin, total cholesterol, and cholesterol esters occurred following the administration of bile salts. However, in view of the values for these substances ob-

tained later in the study, it would seem that these changes may have been not more than a normal variation. The total fatty acid values and their iodine numbers remained practically the same during the administration of the bile salts. The values for the various lipid fractions, after remaining fairly constant, were found to have a tendency to increase following the administration of raw pancreas. The lecithin was not determined at this time, but both the total cholesterol and cholesterol ester values increased, and the same was true of the total fatty acids, while the iodine number of the total fatty acids decreased.

Calcium and Phosphorus Studies.—Under the conditions of an apparently adequate intake of both calcium and phosphorus, we found that the patient was able to store these elements to some extent; and this occurred even though the clinical picture indicated that demineralization had been present for some time in this subject (Fig. 10). The

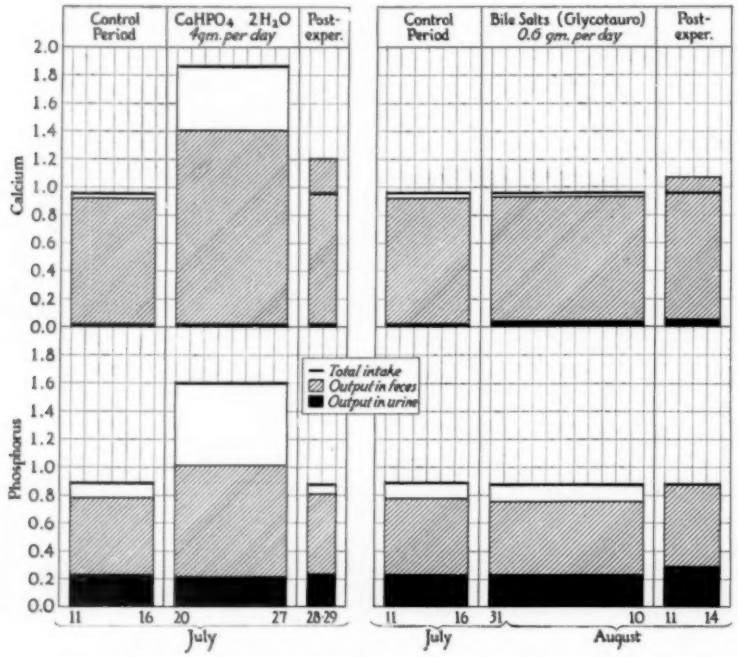


Fig. 10.—The effect of dibasic calcium phosphate and bile salt administration on the calcium and phosphorus balances.

actual retention of calcium was 0.2694 Gm. for this six-day period, amounting to about 2.4 mg. per kilogram of body weight per day. This is about one-third of the minimum that would be expected to be stored by the average child on the same diet under similar conditions. The retention of phosphorus was somewhat greater, being 0.644 Gm. for the

six-day period, or 5.8 mg. per kilogram per day. This is about one-half the amount that probably would be retained by a normal child of a similar age under these conditions.

When the intake of both calcium and phosphorus was practically doubled by the administration of $CaHPO_4.2H_2O$, a definite increase in retention occurred. The amount of calcium retained by this subject was 26 mg., and inorganic phosphorus, 40 mg., per kilogram per day during this eight-day experimental period. As soon as this medication was discontinued, however, we found a large outpouring of calcium in the stool. A slight positive retention of phosphorus was found during this post-medication period. The administration of bile salts did not seem to alter the metabolism of calcium and phosphorus in this subject except for a slight increase in the urinary calcium. In the interval following the discontinuance of these salts, however, a negative balance occurred as regards calcium, while phosphorus seemed to be in balance.

TABLE II

VALUES FOR THE SERUM CALCIUM AND INORGANIC PHOSPHORUS AND THE Ca × P PRODUCT AT VARIOUS INTERVALS THROUGHOUT THE COURSE OF THE STUDY

	10/7/35	5/21/36	5/23/36	7/7/36	10/21/36	1/14/37	2/5/37
Calcium (mg. %)	10.7	13.6	13	12.3	11.2	10.6	10.8
Inorganic phosphorus (mg. %)	5.6	5.5	–	5.6	4.9	4.6	4.4
Product Ca × P	59.9	74.8	–	68.9	54.9	48.8	47.5

No significant changes occurred in the serum calcium and inorganic phosphorus values (Table II). On one occasion a rather high serum calcium value was obtained, but this is of questionable significance in view of the repeatedly normal values found throughout the study. The serum inorganic phosphorus values were also well within normal limits. As mentioned previously, the phosphatase activity of the serum was within the normal range.

DISCUSSION

Although the liver has long been considered the organ of desaturation of the fatty acids, the final proof of this phenomenon is still forthcoming. If there were complete acceptance of this idea of the function of the liver, it would be relatively easy to explain the occurrence of the persistent lipemia in this case. It is not within the scope of this paper to discuss the causes and significance of lipemia; however, it seems indicated, at least, to mention a few of the better known conditions associated with a great increase in the blood fats. As regards the lipemia of diabetes, the mere fact that very little evidence of a disturbance in the carbohydrate metabolism, such as glycosuria, hyperglycemia, or the presence of ketone bodies in the urine, was observed at any time would

tend definitely to rule out the abnormal fat level in the blood as being explainable on the basis of diabetes. Another classical type of lipemia is that associated with so-called lipid nephrosis, again the cause of which is unknown. The absence of albuminuria and hypoproteinemia, as well as there being no possible confusion of the clinical pictures in these two conditions, certainly would prevent one from trying to explain the presence of the excess fat in the serum in this patient on the basis of an obscure nephrosis. The best known type of lipemia, perhaps, is that in which there is the transitory rise in blood fat following a fatty meal. It would be impossible to conceive that this phenomenon has any relationship to this case, as all specimens were taken after an overnight fast. The prolonged use of fat-free diets, as well as high fat diets, has been said to produce increases in the fasting levels of fat in the blood, which factors, even if proved to be true, are not concerned with the lipemia in this case for the dietary composition was not abnormal at any time.

Certain types of lipid storage disease, such as Niemann-Pick and Gaucher's diseases and essential xanthomatosis, are said to be associated with a piling up of certain lipid fractions in the serum. Although this case was associated with the presence of peculiar lipid-laden cells in the lungs, liver, spleen, and bone marrow, it could not be said that the abnormal deposits of fat in the cells were either a primary or secondary phenomenon. The character of the symptoms and the absence of a similar disease in the family, as well as the nature of the blood lipid picture, indicate that this case is not one of the type recently described by Holt, Aylward, and Timbres.[11] Recently we have had the opportunity to study the blood and tissue lipids in a child with a peculiar type of generalized lipodystrophy which was associated with a diabetic picture. This child had the lipemia before the diabetes developed. The lipemia, even though marked, was composed of comparatively little neutral fat, whereas the blood in the child with hepatoma contained enormous quantities of fat present as triglycerides. It is readily apparent that the lipemia in the case we are presenting is not the same type as the one to which we have just referred.

Of interest recently is the work of Dragstedt, Van Prohaska, and Harms,[12] who postulated the existence of a new hormone (lipocaic) in the pancreas which aids in the transport and utilization of fat and tends to prevent the fatty livers present in depancreatized dogs maintained with insulin. Chaikoff and Kaplan[13] found that feeding raw pancreas to depancreatized dogs maintained with insulin caused the blood lipids to rise and the liver lipids to fall. We have no way of knowing what effect the administration of raw pancreas may have had upon the abnormal lipid deposits in the various tissues in our subject. Actually, however, a slight rise occurred in both lecithin and cholesterol, as well as in the total fatty acids of the serum. The exact significance of these

findings is not apparent; however, it seems allowable to suggest that the lack of a pancreatic hormone, or even of a fat-splitting enzyme, from the pancreas does not account for the lipemia in our subject.

Even though we may be able to explain the lipemia on the basis of disturbed hepatic function, it is interesting to speculate on the significance, if any, of a possible relationship of the abnormal metabolism of the fats to the occurrence of the extreme degree of decalcification of the osseous system in this patient. It has been suggested that excess fat in the tissues may actually interfere mechanically with normal deposition of bone. However, this is unlikely in that the histologic appearance of the bone does not bear this out. That both the lipid and osseous systems may be affected by the same factor, such as a hormone, is seen from the work of Landauer, Pfeiffer, Gardner, and Man,[14] who found that, after injecting estradiol benzoate into 6- to 7-month-old cocks, there occurred a deposition of new bone throughout the epiphysis and diaphysis, the serum calcium increased, and at the same time a great change in the lipid constituents of the serum occurred. Much work remains to be done before any drastic statement can be made concerning the interrelationship of the lipid and osseous metabolism, especially in attempting to explain the pathologic picture in this case.

This question naturally leads us to consider the nature and significance of the disturbed metabolism of calcium and phosphorus encountered in this case. In order to simplify somewhat a consideration of the various factors which are known to affect the metabolism of calcium and phosphorus, we have summarized in Table III the most important of these. This does not claim to be a complete list. Naturally we are interested in ascertaining which factors are most likely to cause decalcification of the skeletal system. So far as the clinical aspect of the case is con-

TABLE III

BRIEF SUMMARY OF THE VARIOUS FACTORS WHICH ARE KNOWN TO AFFECT CALCIUM AND PHOSPHORUS METABOLISM

Dietary:
1. Intake of Ca and P and ratio to each other
2. Ash, acid or alkaline
3. Condition of gastrointestinal tract
4. Mineral elements: Pb, Sr, Mg, F, etc.
5. Vitamins D and C

Radiant Energy: ultraviolet, x-rays, radium
Endocrines: parathyroids, pituitary, thyroid, estrogenic hormones, etc.
Enzymes: phosphatase
Tissue Condition: acidosis, alkalosis; inherent dysfunction
Activity: disuse particularly
Fat Metabolism: celiac disease, sprue
Infectious Processes: osteomyelitis, etc.
Tumors: primary and metastatic, Schüller-Christian, leucemia, etc.
Kidney Disease: renal rickets
Liver Function: bile; possible unknown factors

This is not meant to be a complete list.

cerned, this extreme osteoporosis does not seem to fit into any known clinical-pathologic entity.

Obviously, it is not necessary to consider each of these factors in detail. However, mention may be made of some of those more likely to be responsible. Naturally one is confronted with the possibility that decalcification may be due to a prolonged deficient intake of calcium and phosphorus. On the other hand, one is immediately impressed with the great unlikelihood of this in this instance, for a marked degree of demineralization was noted early in the course of the disease, and at this stage, the appetite had remained good. Truly, our mineral balance studies did reveal a slight retention of both calcium and phosphorus when the subject was placed on a more or less ideal type of diet. The amount of these elements retained, however, was but one-third that expected as a minimum for a normal boy of a similar age.[15] In fact, a similar slight retention was found by the authors[3, 4] in the obviously faulty metabolic condition of osteogenesis imperfecta. It can be conjectured readily that a diet which was adequate, yet slightly less than that used in this study, would be associated with a negative balance of both calcium and phosphorus. That this is more than a possibility is again suggested by further balance studies wherein the intake of calcium and phosphorus was practically doubled by the administration of calcium phosphate ($CaHPO_4.2H_2O$). Under these conditions the retention of these elements increased to 26 mg. and 40 mg. per kilogram per day for calcium and phosphorus, respectively. However, as soon as the intake returned to the former, but adequate, level, a marked loss of calcium and a diminution in the retention of phosphorus occurred. It appears, then, that the ability of the osseous tissue to hold these minerals was definitely impaired.

Closely related to this aspect of the problem are the vitamins and hormones. That a deficiency of vitamin D did not exist during this period seems definite from the history of a probably adequate intake of cod-liver oil and exposure to sunlight, as well as from the roentgenologic appearance of the bones. Still more significant is the fact that the levels of both calcium and inorganic phosphorus of the serum throughout the course of the disease at no time showed changes suggesting rickets or osteomalacia. The same reasoning holds true for the endocrine aspect of the problem, especially as regards the possibility of hyperfunction of the parathyroid glands. The normal limits of the levels of calcium and inorganic phosphorus of the serum, of the excretion of urinary calcium, of the phosphatase activity of the serum, and of the reaction of the serum to the parathormone test,[2] and still more significant, the normal appearance of the parathyroid gland on pathologic examination, all speak strongly against excess parathyroid function in this condition. The association of a defective calcium metabolism in such conditions as celiac disease and sprue brings up the possibility of

faulty fat absorption as related to our case. Most significant from this viewpoint is that at no time were fatty or soapy stools seen in our patient. If an abnormal condition of excess fat existed in the intestinal tract in our subject, it might be that the addition of bile salts would favorably affect the absorption and retention of calcium. As regards this point, however, we have noted already that adding bile salts to the diet caused little change in the urinary or fecal calcium and phosphorus, or in the retention of these elements.

From the microscopic and chemical standpoint, we may mention that the histologic appearance definitely reveals that neither a carcinomatous nor an infectious infiltration caused the decalcification of the bony structures in this case. The only finding of note from the microscopic examination of bone was the presence of the same lipid-filled cells seen in certain of the other tissues; yet it does not seem possible that these cells could actually displace the bone-forming tissue, with the consequent loss of the bone-building material from the body. Chemical analysis of the bone obtained from this child, as reported by Hansen, Palmer, and Nelson,[16] revealed an extreme degree of demineralization, which was even more marked than that found in osteogenesis imperfecta, a condition in which the bone is notoriously poorly calcified. More significant was the fact that the ratio $Ca_3(PO_4)_2$:$CaCO_3$ was increased in these bones, indicating that the bone abnormality is analogous to calcium deficiency and not related to rickets, osteomalacia, or phosphorus deficiency.

From a consideration of various factors affecting calcium and phosphorus metabolism, several of which we have discussed, as well as other possibilities, such as the presence of some unknown toxic factor, it seems that none bear any relationship to our case. Thus, we are still unable to explain the pathogenesis of this condition. Of the numerous functions of the liver, many of which are imperfectly understood, that relating to calcium and phosphorus metabolism has not been considered in any great detail. We have abundant proof from our studies mentioned above that liver damage was extensive in this subject. Thus, we may well consider in greater detail to what extent liver function is related to the metabolism of calcium and phosphorus. As long ago as 1904, Pavlov[17] found that osteoporosis developed in dogs with bile fistulas. This observation that exclusion of bile from the intestinal tract leads to bone abnormalities has been confirmed by several workers: Looser,[18] Dieterich,[19] Wisner and Whipple,[20] Buchbinder and Kern,[21] and Greaves and Schmidt.[22] Seidel,[23] in 1910, observed bone atrophy in two human subjects with bile fistula of long duration. As early as 1922 it appeared that some factor other than bile in the liver was related to osseous metabolism. At this time Whipple[1] fed cooked liver to dogs with bile fistula and prevented the occurrence of bony abnormalities. Seifert[24] believed that, in the absence of bile, vitamin D was not absorbed; Klinke[25] postulated that in the lack of bile there is lack of calcium absorption. Tammann[26]

stated that parenteral vitamin D alleviated the condition of osteoporosis due to the absence of bile. Greaves and Schmidt[22] believed that the osteoporosis in dogs with bile fistula developed because of depletion of vitamin D in the bile and that desoxycholic acid may act as a carrier for the absorption of vitamin D across the intestinal membranes, thus eliminating the absorption of vitamin D in the absence of bile. Two years later the same authors[27] found that viosterol administered orally or subcutaneously to jaundiced rachitic rats did not aid calcification as it did in control rachitic animals. In 1935, Taylor, Weld, and Sykes[28] believed that bile was necessary for the absorption of irradiated ergosterol from the gastrointestinal tract. They conducted toxicity experiments in dogs with bile fistula; they observed that when the vitamin D was given by mouth no symptoms occurred, whereas definite toxicity signs were present when the material was given with bile and also with bile salt mixtures, and when administered intravenously.

Hawkins and Whipple,[29] in 1935, stated that the correct explanation for the development of osteoporosis in bile fistula dogs was not known but might be due to the lack of some unknown factor. Gerstenberger[30] offered clinical evidence that, in certain cases of cirrhosis of the liver, rickets developed despite adequate antirachitic measures. This, he believed, was due to some dysfunction of the liver not related to vitamin D or the bile salts. Heymann,[31] in 1937, produced rickets in rats; then he injured the livers in one group of animals by ligating the bile ducts, and in another, by injecting carbon tetrachloride. He found that much larger quantities of vitamin D administered parenterally were required to effect a cure in the rats with the injured livers than in the control rachitic animals. This, he stated, tended to substantiate Gerstenberger's hypothesis that impaired liver function decreases the antirachitic potency of vitamin D.

Another approach to the problem of the possible relationship of the liver to mineral metabolism was first suggested by Nitzescu,[32] who injured the livers of dogs with elemental phosphorus and then injected parathyroid extract; whereupon he failed to obtain a rise of serum calcium in the animals. The inorganic phosphate also remained unchanged. This phenomenon was confirmed by Greenberg,[33] and in further investigation[34] he found that, by poisoning the liver with phosphorus or hydrazine, parathyroid extract administration failed to increase the level of the serum calcium; on the other hand, carbon tetrachloride had no such effect, nor did benzol poisoning prevent this phenomenon. Thus, it was not due to a toxic effect on the bone cells.

We have no evidence that the large number of hepatoma cells are able to produce in excess substances ordinarily present in the liver cells which may affect calcium and phosphorus metabolism, and yet, under abnormal conditions, may cause demineralization to occur. With the above-mentioned facts in mind, together with our inability to explain

our findings in the light of the various factors which are known to affect calcium and phosphorus metabolism, we are confronted with the suggestion that the marked degree of osteoporosis in this case of hepatoma may be due to the lack of some as yet unknown factor normally present in the liver, which has an important effect on calcium and phosphorus metabolism.

Review of the literature concerning primary carcinoma of the liver fails to find any mention made of the condition of the osseous system in this disease, and we are unable to discover any cases with metabolic studies. Cases in adult subjects, though not uncommon, are very malignant. Usually they are of but a few months' duration.[35, 36, 37] In children the disease is much more rare and is likely to run a little longer course, thus giving the opportunity for demineralization to occur at a time when the calcium and phosphorus metabolism is more vulnerable to disturbing influences. Our case is especially unusual in this regard, for the condition probably existed for about two years. As stated, we have been unable to discover similar findings in any reports on this subject. However, a few months after this boy was seen, a child of 8 months was brought to the hospital for study because of the presence of a large, firm mass in the liver area. This child was found to have a lipemia, there being 547 mg. cholesterol and 850 mg. total fatty acid per 100 c.c. serum. Periodic roentgenologic examinations of the skeletal structures revealed a progressive decalcification. The child lived only two months, and at autopsy, a hepatoma was found. Even though the case was of short duration, the findings tend to substantiate our conclusions that destruction of the liver interferes with its ability to function normally in the intermediary metabolism of fats, such as desaturation, which may directly or indirectly lead to lipemia, and that the liver may play an unsuspected role in the intrinsic metabolism of calcium and phosphorus as related to bone.

SUMMARY AND CONCLUSIONS

The report of an unusual case of primary carcinoma of the liver in a 10-year-old child is presented.

The tumor was of the slowly growing but destructive type, causing impairment of certain liver functions without causing measurable jaundice until near the end of life.

The most striking clinical features were marked lipemia with extensive lipid histiocytosis of various organs and extreme osteoporosis. Chemical and histologic examination of the bones showed that the osteoporosis was not due to lipid infiltration.

Results of a mineral balance study indicate that the extreme osteoporosis was due to defective retention of calcium and phosphorus by the osseous system.

Since this defect in retention manifested itself despite an adequate intake of vitamin D and without evidence of hyperparathyroidism or impairment of absorption of calcium and phosphorus from the gastrointestinal tract, it was tentatively concluded that the liver normally plays an essential role in osseous metabolism. It would appear that this function was seriously impaired in the present case.

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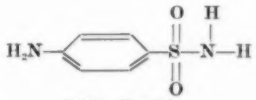
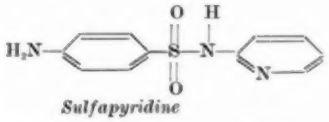
THE TREATMENT OF ACUTE STAPHYLOCOCCIC INFECTIONS WITH SULFAMETHYLTHIAZOL

DONALD WEISMAN, M.D., AND HOLLIS RUSSELL, M.D.
WHITE PLAINS, N. Y.

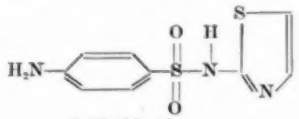
ONE of the latest additions to the group of antibacterial chemotherapeutic agents is the methyl derivative of sulfathiazol, the analogue of sulfapyridine, designated as sulfamethylthiazol. The following formulas show its chemical relations to sulfanilamide, sulfapyridine, and sulfathiazol:



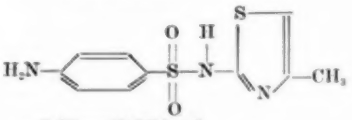
Sulfanilamide



Sulfapyridine



Sulfathiazol



Sulfamethylthiazol

To date, there are reports[1] in the literature on the chemistry of sulfamethylthiazol and sulfathiazol and reports on their chemotherapeutic effects. The publication by Barlow and Homburger[1] indicated that sulfamethylthiazol is highly effective against staphylococcus, as well as certain other pathogenic bacteria. One successfully treated case of staphylococcus bacteriemia has been reported by Herrell and Brown[2] and two others by Carroll and associates.[3] The latter also described briefly the use of the new drug in three patients suffering from less serious types of staphylococcus infection. Pool and Cook[4] have reported the successful use of the drug in infections of the urinary tract.

From the Pediatric Service and Department of Pathology, St. Agnes Hospital.

Sulfamethylthiozol* was administered by us to five infants with acute infective laryngotracheobronchitis, three of whom required tracheotomy.

The prognosis in such cases is grave. Jackson and Jackson[5] state, "Recovery occurs in not more than 50 per cent of the cases under the best possible conditions," and say further that "the prognosis is unfavorable inversely as the age of the child."

CASE 1.—W. L., a boy, aged 2 years, was brought to the hospital on Jan. 17, 1940, with the complaint of difficult breathing. The onset had been four days prior to admission, and the course had been one of steadily increasing severity. It was apparent that the boy was acutely ill and in great respiratory distress. There was marked suprasternal, sternal, and substernal retraction; with each inspiratory effort, the entire anterior thoracic cage was thrown violently inward. The skin was ashen and the lips violet. The temperature was 102.6° F., and the pulse rate, 150. Direct laryngoscopy revealed the characteristic picture of acute laryngotracheobronchitis.

Immediate tracheotomy was deemed necessary as a lifesaving measure. Upon incision of the trachea, a large amount of tenacious white pus, apparently under pressure, filled the wound. Instant relief from the respiratory distress was afforded by the operation.

Neoprontosil was given parenterally in the hope of alleviating the desperate condition, even though the character of the pus at operation indicated that the infection was caused by staphylococcus. (Direct tracheal cultures taken at the time of operation later showed a pure growth of hemolytic *Staphylococcus albus.*) A roentgenogram of the chest after operation revealed a collapsed left lung. Oxygen was administered, epinephrine (in dilute solution) instilled into the tracheotomy tube at frequent intervals, and suction applied every twenty minutes during the day and night. Despite these measures, the boy's condition grew progressively worse. Two days postoperatively he was weaker, the respirations were more labored, and inspiratory retraction was more marked. The boy appeared more toxic. On the fourth day these ominous signs were more pronounced; he was hard to arouse and could not be persuaded to take nourishment. The temperature during these four days was between 102 and 103° F., and the pulse rate, 150.

At this point, sulfamethylthiazol was obtained. Following the administration of this agent, a striking change was observed. Treatment was started at 3:00 P.M. on January 21. The next morning the child was brighter and appeared less toxic, and the breathing was better. By the afternoon of this day, the temperature had decreased to 99° F. On the next day there was still greater improvement, the patient being alert and cooperative; the following day he played and smiled and appeared to have recovered from the infection and to be entering the convalescent stage.

During convalescence, the temperature remained below 100° F., with one important exception. The daily dosage of sulfamethylthiazol had been varied in accordance with the determinations of the concentration of the drug in the blood. After six days of therapy, an attempt was made to reduce the dosage because of the clinical improvement which had taken place and the appearance of a mild toxic rash (apparently not due to the drug). Upon reduction of the dose, the temperature rose to 103° F.; with increased dosage, the temperature promptly fell to 99° F. The rash, which had disappeared, did not return. After thirteen

*We express gratitude to the Department of Medical Research, Winthrop Chemical Company, Inc., for supplying sulfamethylthiazol at a time when this drug was available in very limited amounts.

days of administration, the drug was discontinued (February 3). The child was observed for fourteen days longer, during which time there was no fever nor any other sign of infection. The tracheotomy tube which had been corked for progressively longer intervals, beginning five days after the institution of sulfamethylthiazol therapy, was finally removed on February 2.

CASE 2.—R. M., a 7-month-old boy, was admitted on Jan. 25, 1940, in acute respiratory distress which had first been noticed twelve hours previously. The general condition closely resembled that of Case 1. Tracheotomy was performed and gave instant relief. Cultures taken at operation later showed a pure growth of *Staphylococcus aureus*, consisting of hemolytic and nonhemolytic types. Because of the severity of the toxemia, which appeared to be increasing in intensity, and a return of respiratory distress, it was deemed advisable to administer sulfamethylthiazol. The drug was started fifteen hours after tracheotomy was performed, and an attempt was made to give it in adequate dosage from the beginning. Except for one period of difficult respiration about twelve hours after the initial dose, improvement rapidly followed. Within thirty-six hours, the temperature decreased from 104 to 99.4° F. Improvement continued, and it was possible to remove the tracheotomy tube on January 30. Drug therapy was discontinued on February 3. Except for a recurrence of fever (maximum 101° F.) for one day (February 5), recovery was uneventful.

CASE 3.—R. B., a 5-month-old boy, was admitted on Jan. 18, 1940, with a history of difficult respiration of eight hours' duration. The condition was not as severe as that encountered in the previous cases. There was respiratory distress, but tracheotomy was not required. Forty-eight hours after admission the patient was worse; the temperature was rising, and respiratory distress was increasing in severity. The throat culture growth was reported to consist of hemolytic *Staphylococcus albus* (about 80 per cent) and *Streptococcus viridans* (about 20 per cent). Sulfamethylthiazol therapy was started on January 21. The temperature fell rapidly, and there was definite improvement twenty-four hours later. In another day the change for the better was very striking. Respiration was entirely normal after six days of treatment. On January 30, the patient was discharged.

CASE 4.—P. W., a 21-month-old male infant, was admitted on March 2, 1940, in acute respiratory difficulty. The temperature was 103° F. A tracheotomy was performed at once. Direct tracheal culture revealed a pure growth of *Staphylococcus albus*. Sulfamethylthiazol therapy was instituted immediately. The temperature was 99° F. within twelve hours, and the patient was much improved. There were periods of respiratory distress during the next few days, and supportive measures were employed. These included the use of an oxygen tent. Respiration was normal after five days of treatment.

CASE 5.—J. D., a 4-year-old boy, was admitted on Feb. 29, 1940, with the complaint of increasingly difficult breathing. A throat culture showed 80 per cent *Staphylococcus aureus* and 20 per cent nonhemolytic streptococcus. Dyspnea and sternal retraction were rapidly becoming more marked. However, tracheotomy was deferred because of the presence of a long-standing nephrosis. There was generalized edema, and the patient appeared to be a poor operative risk.

Sulfamethylthiazol therapy was started, and improvement was noted in about five hours. The symptoms subsided completely about forty-eight hours later.

On admission, the urine contained leucocytes, erythrocytes, albumin, and casts. Repeated urinalyses showed no deviations from the admission findings, either during or after treatment. There was distinctly less edema on discharge. Sulfamethylthiazol apparently had had no deleterious effects upon the kidneys.

We administered sulfamethylthiazol to two other children with acute staphylococcus infections. Both had bacteriemia. There are a few reports in the literature on recovery from this disease. Schlutz[6] says, "It is, however, a fact that, of all septicemias occurring in children, those due to the staphylococcus are the most serious. Hemolytic staphylococcic septicemia is the most virulent form of septicemia encountered in childhood."

CASE 6.—R. M., a boy aged 6 years, was admitted on Feb. 10, 1940, with bilateral acute purulent otitis media. Myringotomy was performed on both sides. The cultures from the ears showed nonhemolytic streptococcus on the left and hemolytic *Staphylococcus aureus* on the right.

The next day the general condition appeared worse. It was noted that both mastoid areas were tender on slight pressure and that the temperature was again elevated. The patient complained of severe knee and ankle pains, and these joints were swollen, red, and markedly tender. The blood showed a pure growth of hemolytic *Staphylococcus aureus.* Sulfamethylthiazol therapy was instituted at 3 P.M. on February 11. The temperature fell to 100° F. by midnight, and joint pain was relieved.

The next morning (February 12), the patient appeared to be far better. The temperature was 99.6° F., the appetite was good, and the patient was alert. The mastoid regions were distinctly less sensitive to pressure. The sagging of the posterior canal walls was less marked. Improvement was rapid and progressive. Repeated blood cultures failed to show any growth.

A generalized rash was noticed on February 21, the tenth day of sulfamethylthiazol treatment. Administration of the drug was promptly discontinued. The rash had largely disappeared in twenty-four hours, and completely so in forty-eight hours.

It had been assumed that the mastoid areas would require drainage, but operative interference was deferred daily because of the obvious improvement. Surgery was finally deemed unnecessary. The patient was discharged after a hospital stay of sixteen days, showing no signs of infection.

CASE 7.—A. E., a 9-year-old boy, was admitted on Feb. 18, 1940, with the diagnosis of fulminating osteomyelitis of the right femur. Immediate operation was performed. Cultures of a subperiosteal abscess and of the medulla of the femur were taken in the operating room. A blood culture was obtained at the same time. These cultures and another blood culture taken the following day contained pure growths of *Staphylococcus aureus.*

The temperature was of the intermittent type, reaching a high point of 107° F. The patient complained bitterly of intense pain in the left knee. He had obviously embarked upon the stormy course characteristic of acute osteomyelitis complicated by bacteriemia.

The administration of sulfamethylthiazol was started at 3 P.M. on February 19. The next morning remarkable improvement was apparent. The temperature decreased by lysis, and the only complaint was of pain in the wound. A number of blood cultures taken since the institution of sulfamethylthiazol therapy have been negative. The patient is now undergoing an uneventful convalescence from the osteomyelitis.

DISCUSSION

Dosage of Sulfamethylthiazol.—According to the experimental findings of Barlow,[1] a blood concentration of at least 5 mg. per cent is prob-

ably the optimal therapeutic level of this drug. In our experience, this value was secured with dosages ranging from 1½ grains (0.09 Gm.) to 3 grains (0.19 Gm.) per pound of body weight per twenty-four hours. In Case 1, the initial dosage was 1⅓ grains per pound, which resulted in a blood concentration of 1.42 mg. per cent. With an increase in dosage to 2⅓ grains per pound, the level rose to 2 mg. per cent; a still further increase to 3 grains per pound raised the level to 4.34 mg. per cent. In Case 4, a blood concentration of 9.5 mg. per cent was obtained by a dosage of 2½ grains per pound.

Our clinical results indicate that blood levels of from 5 to 10 mg. per cent are unnecessarily high. We have obtained very satisfactory responses with blood drug concentrations of from 2 to 5 mg. per cent. It is possible that still lower concentrations may be effective.

As with other sulfonamide drugs, it appears that treatment can be satisfactorily carried out by the administration of doses which clinical experience has demonstrated to be efficacious. However, the resorption capacity after oral medication varies widely in different persons. It can be determined accurately only by daily blood analyses, and this guide should influence the judgment of dosage variations. Thus, reliable clinical orientation may be received from the laboratory, and failures due to inadequate dosage can be obviated.

We have found that the determination of sulfamethylthiazol can be facilitated by substituting trichloracetic acid for alcohol. This modification in the standard procedure results in a clear solution, and, hence, obviates the need for filtration before the final colorimetric comparison.

Toxicity.—Subjective symptoms when present were trivial. The erythrocyte count and the hemoglobin have gradually decreased during treatment in most of the cases observed by us. These decreases have never been alarmingly sudden. The total leucocytes and the percentage of neutrophiles have not been affected adversely. No evidence of kidney damage was noted.

On our medical service, a case, treated with our cooperation, presented weakness of the hands and foot drop, with difficulty in walking, which we attribute to the therapy. We are grateful to the Department of Medical Research of the Winthrop Chemical Company for informing us that others working with sulfamethylthiazol have reported to them some cases of peripheral neuritis developing during the course of, or consequent to, the use of this drug. It appears that the incidence may be as high as 1 per cent. It is therefore obvious that the use of this agent should be confined to fulminating cases of staphylococcus infection, and perhaps only to those patients with demonstrable bacteriemia. Under no circumstances should it be given without adequate control measures. Routine determinations of the concentration of the drug in the blood and

frequent studies of the condition of the various blood elements will not only help to prevent the occurrence of anemia and leucopenia, but possibly, by this means, some of the cases of neuritis may be avoided. Thus, with the discovery of unusually high concentrations, immediate reduction in dosage or cessation of treatment is indicated.

No case of peripheral neuritis, or even any suggestion of this condition, has been encountered in the infants and children treated by us. We have been informed also that this complication has not occurred in several hundred infants and children treated by others. At one large clinic there have been over two hundred cases of severe staphylococcus infections, pneumonia, and a variety of other types of infection in infants and children treated with sulfamethylthiazol. Peripheral neuritis was not observed.* Perhaps this type of chemical neuritis is an affliction of adults only. It is well known that such lesions cannot be produced experimentally in animals. It may be that the tolerance to sulfamethylthiazol is greater in infants and children than it is in adults.

Great interest now attaches itself to sulfathiazol, the unmethylated substance. Generally speaking, methylated compounds are toxic. It is our plan to continue our investigations with sulfathiazol, which is also highly effective against staphylococcus.

SUMMARY

Five cases of acute infective laryngotracheobronchitis in infants and two cases of staphylococcus bacteriemia in children, which were treated with a new sulfonamide drug (sulfamethylthiazol), are briefly described. With dosages varying from 1½ grains (0.09 Gm.) to 3 grains (0.19 Gm.) per pound of body weight per twenty-four hours, a satisfactory and effective concentration of the drug in the blood was obtained. The clinical response to the medication in these severe staphylococcus infections was striking.

An improvement in the method of determining blood drug values is mentioned.

Experiments on absorption and excretion are now in progress. The possibility of the occurrence of peripheral neuritis, which, to date, has been observed only in adults, and its bearing upon the use of sulfamethylthiazol are discussed.

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170 Maple Avenue

30 Old Mamaroneck Road

METHEMOGLOBINEMIA FOLLOWING SULFANILAMIDE AND SULFAPYRIDINE THERAPY IN INFANTS AND CHILDREN

BENJAMIN W. CAREY, M.D., AND JAMES L. WILSON, M.D.
DETROIT, MICH.

THE studies of Hartmann, Perley, and Barnett,[1] Harris and Michel,[2] Wendel and Wendel,[3] and Vigness, Watson, and Spink,[4, 5] have satisfactorily shown that the cyanosis observed during sulfanilamide therapy is due to the formation of methemoglobin, and rarely sulphemoglobin, in the circulating blood. The estimations of methemoglobin and sulphemoglobin concentrations were made with the spectrophotometer by all of these workers. Evelyn and Malloy[6] have published a method for the quantitative determination of oxyhemoglobin, methemoglobin, and sulphemoglobin on a 0.1 c.c. sample of whole blood with the Evelyn photoelectric colorimeter. The concentration of "free" sulfanilamide or sulfapyridine in the same 0.1 c.c. blood sample may be estimated by using the micromethod of sulfanilamide determination reported by MacLachlan, Carey, and Butler.[7]

The previously quoted reports on methemoglobin formation have shown studies of the relation of the concentration of methemoglobin to the total hemoglobin and to the dose and blood levels of sulfanilamide and sulfapyridine. Hartmann and his co-workers[1] concluded that there was marked individual variation in both the rate and degree of methemoglobin formation during sulfanilamide therapy in infants and children, but that the dosage of sulfanilamide and its blood concentration seemed to have a direct relationship to the methemoglobinemia. Harris and Michel[2] stated that the average methemoglobin value of all bloods was proportional to the sulfanilamide concentration. Vigness, Watson, and Spink[5] gave no results as to the relation of the amount of methemoglobin to the blood concentration of sulfanilamide of adult patients, but stated that neither cyanosis nor methemoglobinemia was noted following sulfapyridine therapy, whereas Harris and Michel[2] found cyanosis and methemoglobinemia following sulfapyridine administration, although the amounts were less than those observed following sulfanilamide.

Questions continually arise about the relationship of the dose of sulfanilamide or sulfapyridine to the blood levels of the "free" amounts of these substances. Many workers have suggested that the effective blood level of "free" sulfanilamide should be between 8 and

From the Children's Hospital of Michigan and the Department of Pediatrics, Wayne University College of Medicine.

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12 mg. per cent, and the dose necessary to maintain this amount was about 1 grain per pound of body weight each twenty-four hours.

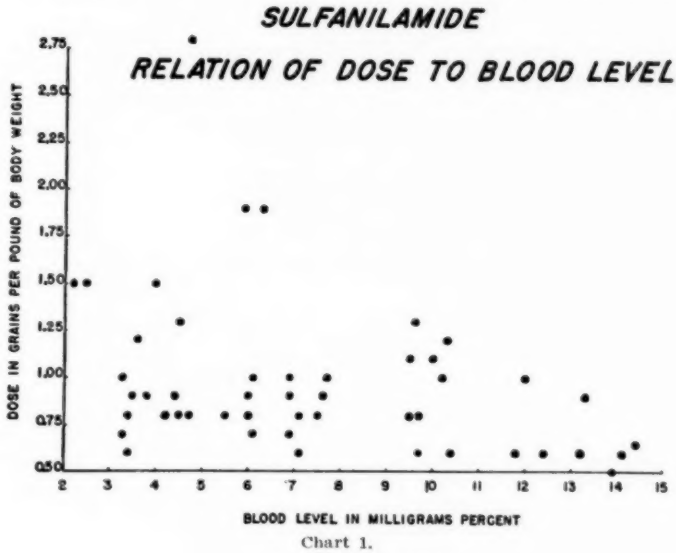

Chart 1.

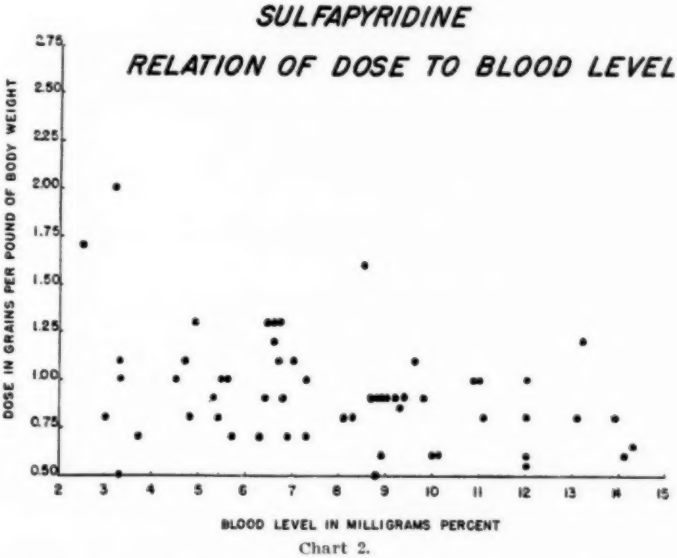

Chart 2.

Definite proof is lacking as to the effective level of "free" sulfapyridine, but various writers have suggested a minimum level of 4 mg. per cent.[8, 9] It was shown by Carey and Cooley[9] that there may

be considerable variation in the average blood levels of "free" sulfapyridine in infants and children.

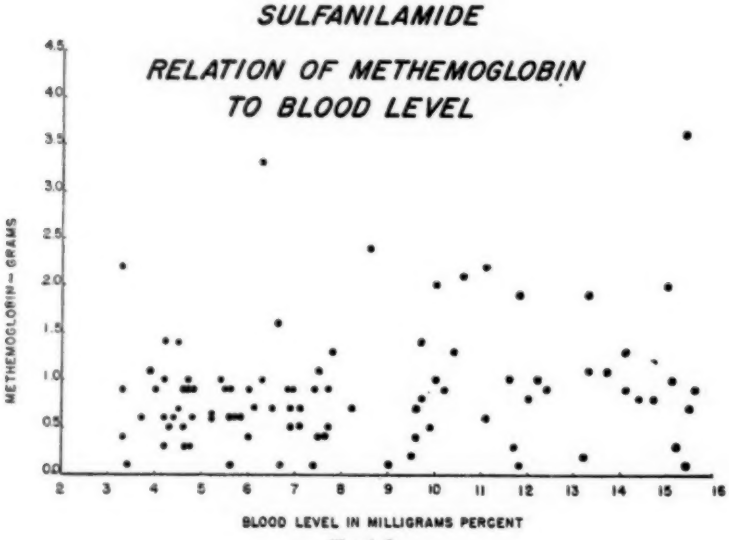

Chart 3.

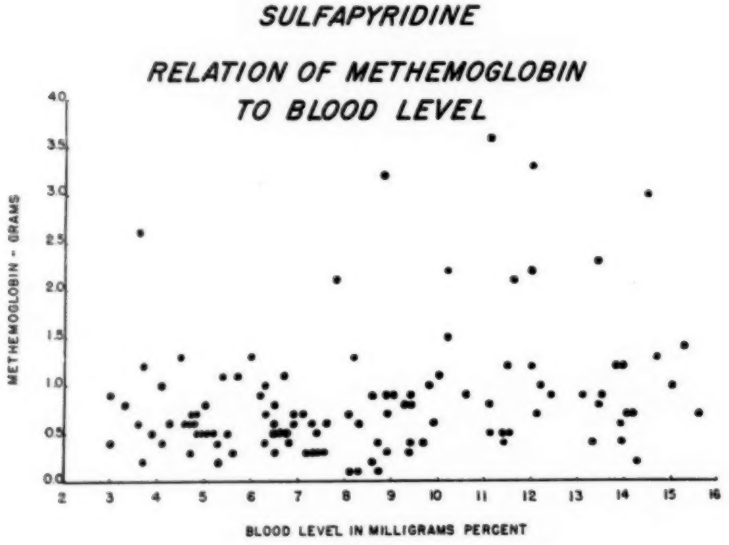

Chart 4.

The data on infants and children are presented in an attempt to show the relation of the dose of sulfanilamide or sulfapyridine to the blood

levels of these substances and to the amounts of methemoglobin and total hemoglobin. All determinations were made by the Evelyn photoelectric colorimeter, using a 0.1 c.c. sample of whole blood obtained by finger-

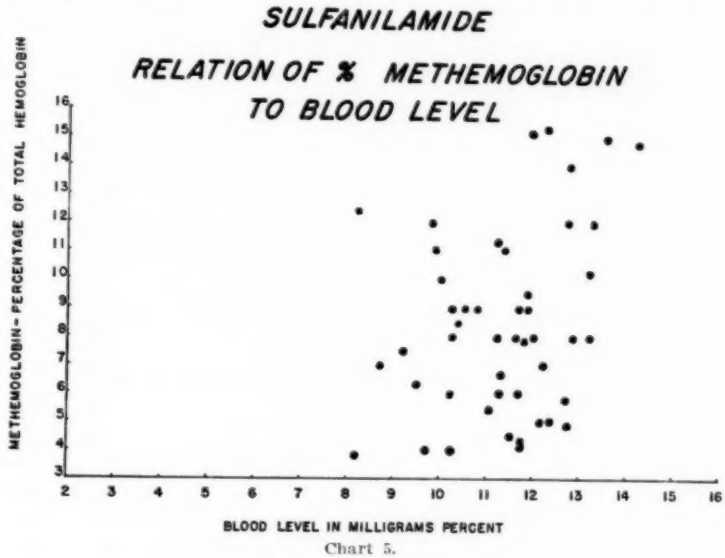
SULFANILAMIDE
RELATION OF % METHEMOGLOBIN TO BLOOD LEVEL
METHEMOGLOBIN - PERCENTAGE OF TOTAL HEMOGLOBIN
BLOOD LEVEL IN MILLIGRAMS PERCENT

Chart 5.

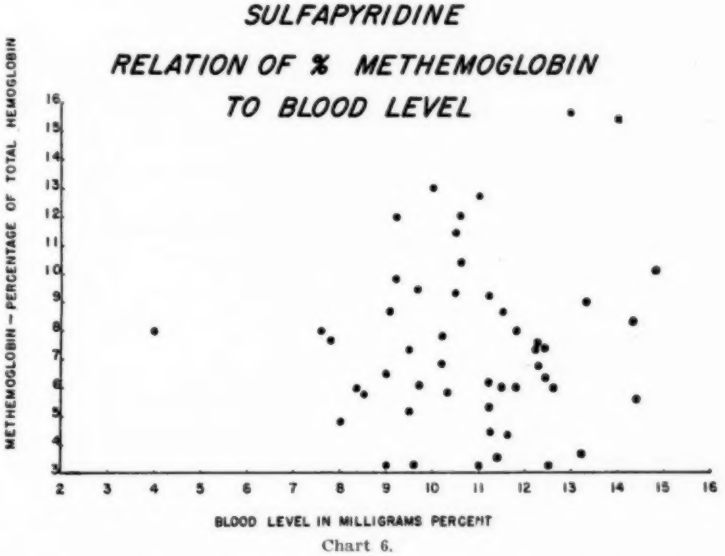
SULFAPYRIDINE
RELATION OF % METHEMOGLOBIN TO BLOOD LEVEL
METHEMOGLOBIN - PERCENTAGE OF TOTAL HEMOGLOBIN
BLOOD LEVEL IN MILLIGRAMS PERCENT

Chart 6.

prick. The data were taken from the charts of the patients, always omitting the first and last estimation, that is, at times before equilibrium

of the blood level had taken place, or after the drugs were stopped. All values for sulfanilamide and sulfapyridine are for the "free" substances.

Charts 1 and 2 show the relationship between the dose per pound of body weight of sulfanilamide and sulfapyridine to the blood level of the drugs. In each case, there is surprisingly little relationship, high blood levels existing with low dosage, and vice versa.

Charts 3 and 4 show the relationship between the methemoglobin level and the blood level of sulfanilamide and sulfapyridine. The number of cases without the presence of methemoglobin is very small. However, there is no very definite tendency toward an increasing amount of methemoglobin with increasing elevation of the blood level.

Charts 5 and 6 show the percentage of the total hemoglobin changed to methemoglobin at different blood levels of sulfanilamide and sulfapyridine. We see a wide range of percentages of methemoglobin at the different blood levels. There is apparently only a slight tendency for increased methemoglobin as the blood level increases.

SUMMARY AND CONCLUSIONS

Data from infants and children have been presented in an attempt to correlate the dose of sulfanilamide and sulfapyridine and the blood level, the relation of the methemoglobin level of the blood and the blood concentration of sulfanilamide and sulfapyridine, and the relation of the percentage of the total hemoglobin changed to methemoglobin at different blood levels of the drugs.

There is apparently little relationship between the dose of each of these drugs and the blood levels of the "free" amounts of the substances. Several factors, as yet unproved, may be responsible: First, there may be marked fluctuations and individual variations in the degree of acetylation in the body of these drugs, resulting in variable amounts of "free" substance; second, absorption from the gastrointestinal tract may normally be quite variable in individual patients; third, absorption may be influenced both by the severity of the infection for which the drug is given, and by the time of administration of the drug in relation to previously ingested fluids or food; and fourth, the rate of urinary excretion may be widely variable.

There seemed to be no definite relation between increasing amounts of methemoglobin and increasing blood concentrations of "free" sulfanilamide and sulfapyridine. However, methemoglobinemia was observed in almost every patient who received sulfanilamide or sulfapyridine.

In comparing the percentage of the total hemoglobin changed to methemoglobin at different blood levels of sulfanilamide and sulfapyridine, the tendency toward increasing the percentage of the methemoglobin as the blood levels increased was only slight.

Although not quantitatively presented with these data, amounts of sulphemoglobin, in addition to methemoglobin, were occasionally noted in the bloods of this group of patients, but in no instance was the amount of sulphemoglobin as great as that of methemoglobin.

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A CLINICAL STUDY OF THE WELTMANN SERUM COAGULATION REACTION

SUSAN COONS DEES, M.D.
MINNEAPOLIS, MINN.

INTRODUCTION

THE serum coagulation reaction developed in 1930 by Oskar Weltmann[1] as a means of differentiatng inflammatory from fibrotic processes has found a place as a diagnostic aid in many European clinics. Since it has been employed very little in America, it is hoped that the present report will serve to stimulate interest in determining its true value.

Prior to Weltmann's work, it had been shown that the temperature at which human serum coagulates varies in different types of diseases and is influenced by electrolyte concentration in the serum and the diluent.[2-12] In his first contribution, Weltmann showed that normal serum, diluted 1:50 with distilled water, remained clear after boiling in contrast to the serum from patients with cirrhosis of the liver, which showed turbidity under the same conditions. Dilution with tap water or physiologic salt solution produced turbidity in normal serum at 100° C., while serum from patients with cirrhosis of the liver showed frank flocculation at this temperature. Flocculation could be produced with normal serum diluted 1:50 with distilled water after the addition of one drop of a 10 per cent solution of either $CaCl_2$, $BaCl_2$, $MgCl_2$, or $(NH_4)_2SO_4$. Salts with trivalent cations had an even more striking effect upon flocculation. On the basis of these observations, a test was devised which consisted of boiling dilute serum in the presence of varying concentrations of electrolytes.

TECHNIQUE

The standard technique, as devised by Weltmann, is as follows: Ten dilutions of $CaCl_2.6H_2O$ solutions ranging from 0.1 per cent to 0.01 per cent are made up from a stock solution of 10 per cent $CaCl_2.6H_2O$. The dilutions are numbered from one to ten, beginning with the most concentrated. Five cubic centimeters of each dilution are measured into ten small test tubes which are numbered to correspond to the dilutions. To each tube is added exactly 0.1 c.c. of unhemolyzed serum. After the contents of the tube are thoroughly mixed, the tubes in their rack are immersed in a boiling water bath for fifteen minutes. At the end of this

From the Department of Pediatrics, University of Minnesota.

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time they are removed, and the highest dilution at which flocculation is present is noted. Flocculation rather than turbidity is taken as the end point, since Weltmann found that normal serum constantly gave flocculation in the first six tubes, that is, through a concentration of 0.05 per cent calcium chloride. The number of tubes showing turbidity may be quite variable, and the degree of turbidity is difficult to estimate. The six tubes showing flocculation constitute the normal coagulation band, or C.B. = 6. Occasionally, normal serum shows partial flocculation in the seventh tube, and this is expressed as C.B. = 6½. In order to have a sharp end point in sera of this type, Weltmann suggested the use of a 0.045 per cent dilution, calling this tube 6½, making a total of eleven dilutions instead of ten. Micromethods and other modifications to simplify the test or to reduce the amount of serum or equipment have been suggested by several authors.[13, 14, 15]

CLINICAL APPLICATION

Despite the meager knowledge of the fundamental phenomena concerned in the production of the coagulation band, the Weltmann reaction has been studied extensively from a clinical point of view, with the accumulation of considerable empirical data. The normal band of 6 or 6½ is a remarkably constant finding. The values as given by independent observers for various diseases likewise show striking agreement. In a series of papers, Weltmann and his colleagues studied the coagulation band in different diseases.[1, 16, 17] From their results they concluded that the test, while being nonspecific, has its chief value in distinguishing between acute infectious and fibrotic processes. In active infection, flocculation rarely occurs in the sixth tube, but tends to be confined to the first few tubes of the series. This is termed a "shift to the left" of the coagulation band. In chronic fibrotic processes, on the other hand, the coagulation band is prolonged, so that flocculation occurs in the higher dilutions up to tube nine or ten. This is designated as a "shift to the right." For example, in lobar pneumonia, the coagulation band is ordinarily zero, with no flocculation in any tube. In cirrhosis of the liver, however, the coagulation band is frequently as high as 9 or 10. When exudative and fibrotic processes occur simultaneously, the coagulation band is influenced by both processes and reflects the balance between the two conditions.

The Weltmann reaction has received most attention in connection with pulmonary tuberculosis.[18, 43] In 2,444 reported cases in which the test has been performed, all authors agree that there is a definite "shift to the left" in acute, ulcerative pulmonary tuberculosis, and that with healing, the band returns to normal or shifts slightly to the right. The presence or absence of this "shift to the right" is considered of great prognostic value in following the course of the disease. In ob-

serving the progress of acute rheumatic fever, the same general information is obtained.[26, 44, 45] During the early stages, when inflammatory and exudative signs are prominent, the band shifts to the left, and when the acute process subsides, there is a return to normal values. If fibrotic changes, such as cardiac valvular damage or chorea, develop, the band may become prolonged above normal levels.

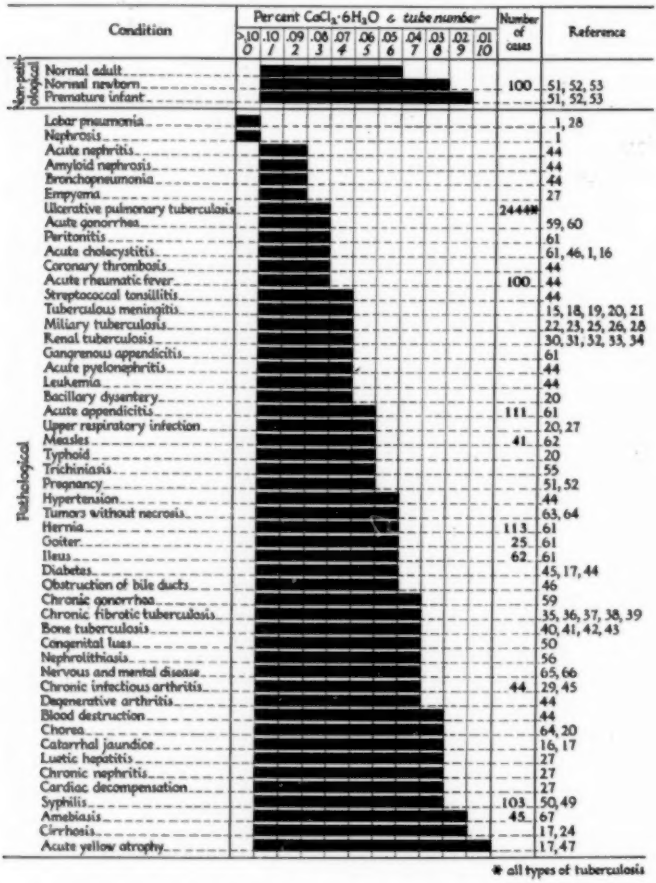

Fig. 1.—Ranges of coagulation band in various diseases as reported in the literature.

The Weltmann reaction also has been used extensively in the study of liver disease.[1, 16, 17, 24, 27, 29, 46, 47, 48] It has proved of value in differentiating conditions in which there is liver damage from those in which there is merely retention of bile. In cirrhosis of the liver, acute yellow atrophy, and toxic hepatitis, the band is prolonged to 9 or 10. On the other hand, in jaundice due to obstruction of the biliary tract

by stone, or carcinoma, the band is frequently normal. In catarrhal jaundice, the band may be slightly shorter than normal, or rarely as high as 7 or 8.

A tabulation of the reported values for the coagulation band in various representative diseases has been compiled from the literature. For the sake of brevity, the summarized data are presented in graphic form (Fig. 1). Whenever stated by the authority, the number of cases upon which the determinations were made has been recorded. The average reported values have been taken and are shown in the chart. The numbers in the column marked "Reference" refer to the bibliography.

The Weltmann reaction has given valuable information in certain conditions primarily of interest to the pediatrician. One finds that much of the data on tuberculosis has been obtained from youthful cases. Zambrano[31] states that the reaction was of prognostic value in a series of thirty-two infants with different types of tuberculosis. He believes that the reaction is not affected by simultaneously occurring congenital syphilis. However, in congenital syphilis the coagulation band is characteristically between 7 and 8.[49, 50] The value of the test in acute rheumatic fever has already been mentioned. In normal newborn and premature infants the coagulation band is markedly prolonged, up to 8 or 9, while maternal blood at the time of delivery, if the pregnancy is uncomplicated, shows a coagulation band of 6.[51, 52, 53] The coagulation band is apparently more easily shifted to the left as a result of acute infection in the child than in the adult. This may be due, in part at least, to pre-existing fibrotic processes in the older subject which may tend to keep the value at falsely high levels.[44]

RESULTS FROM A STUDY OF 246 ADDITIONAL CASES

The results of tests done on a series of 246 patients at the University of Minnesota Hospital, representing a variety of diseases, are presented in Fig. 2. In the figure, the range of reaction predominantly found is shown by solid black; extension of reaction beyond that usually encountered in an occasional case is indicated by shading. The findings in this series agree, in general, with the values reported in the literature. The acute infections assumed a position low in the scale; the less severe infections and more chronic ones had somewhat longer bands. Allergic diseases, as a group, were normal or showed slight shifting to the left, while metabolic diseases, such as obesity, glandular dyscrasias, and uncomplicated diabetes, had prolonged bands. Cardiac decompensation and purpura generally had bands extending well above normal.

The majority of cases consisted of acute rheumatic fever and acute appendicitis. In these two groups an attempt was made to compare the coagulation band with the white blood count and the sedimentation

rate. It was found that there was no significant correlation between these values. However, even though the values for the white blood count and the sedimentation rate could not be predicted from the

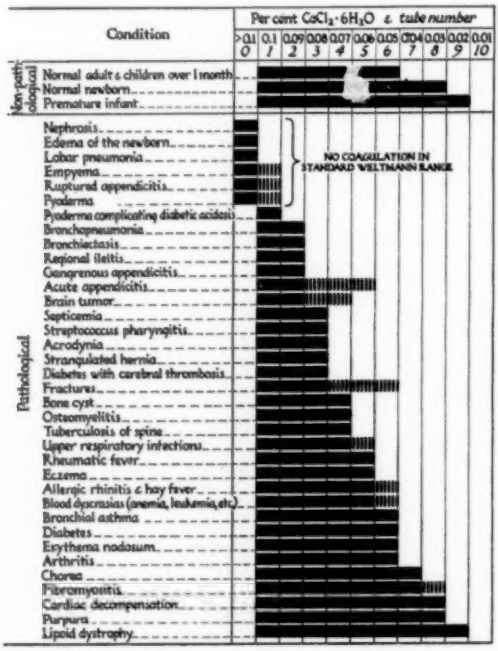

Fig. 2.—Analysis of coagulation bands in 246 patients from the Pediatric Service of the University of Minnesota Hospital.

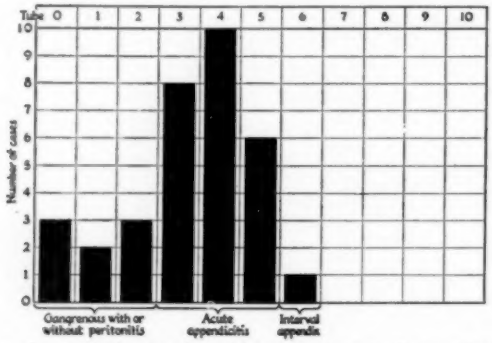
Tube 0 1 2 3 4 5 6 7 8 9 10
Number of cases
0 1 2 3 4 5 6 7 8 9 10
Gangrenous with or without peritonitis
Acute appendicitis
Interval appendix

Fig. 3.—Range of coagulation band in thirty-three cases of appendicitis in children.

coagulation band, it was apparent that, in cases with a very short coagulation band, the white blood count was very much elevated and the sedimentation rate was increased.

Fig. 3 illustrates the range of the coagulation band in thirty-three cases of appendicitis, the diagnosis in all being confirmed at operation. A division could be made between the cases of gangrenous appendicitis with or without peritonitis, with a coagulation band of from 0 to 2, and the cases of acute appendicitis, with a coagulation band of from 3 to 5. In the latter group, the coagulation band was frequently shifted to the left at the onset of symptoms when physical signs were minimal or equivocal and before either the white blood count or the sedimentation rate was altered. For this reason, a decrease in the coagulation band in the presence of symptoms and signs suggestive of acute appendicitis may well be a significant early laboratory finding. When symptoms are of long duration, when physical signs are classical, or when the white blood cell count is elevated, the coagulation band is much less likely to give additional information.

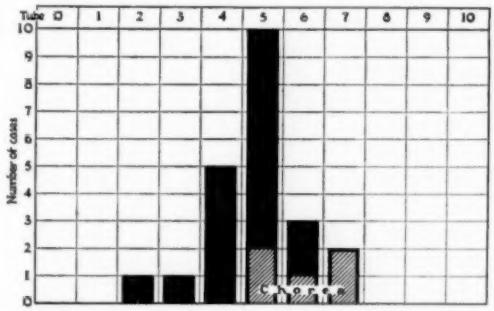

Fig. 4.—Range of coagulation band in twenty cases of rheumatic infection and five cases of chorea.

A similar analysis of twenty cases of rheumatic fever and five cases of chorea with respect to the range of coagulation band is shown in Fig. 4. It will be seen from the chart that the majority of cases had a coagulation band of from 4 to 5. This is a definite, though not a striking, shortening in the coagulation band and is accompanied by an increase in the white blood cell count and the sedimentation rate. All of these were severe cases requiring hospitalization, many with well-developed valvular lesions. None of the patients were seen at the onset of their symptoms. It is impossible, therefore, to say whether or not an early drop in the coagulation band might have been found to precede the other changes in the blood picture, as in the cases of appendicitis.

DISCUSSION

Because of the increasing interest in the Weltmann reaction as a nonspecific test for disease activity, further knowledge regarding its practical limitations and the physiologic or chemical mechanism involved in its development is greatly needed. The nature of the phenomena underlying the reaction is not clearly understood. Weltmann

suggested that alterations in the coagulability of the serum albumin by heat and salts furnished an explanation of the coagulation band.[1] However, the albumin content of the serum is not the sole controlling factor, since frequently a 1:100 dilution has a longer band than a 1:50 dilution.[54-58] That the length of the coagulation band is not dependent merely upon the levels of the serum proteins is evident from the fact that the bands characteristic of different diseases may vary widely, even though the values of the serum proteins are identical. For example, a patient with lobar pneumonia with a coagulation band of zero may have the same amount of total serum protein and the same albumin-globulin ratio as a patient with hepatic cirrhosis with a coagulation band of 9.

The presence of bile in the serum apparently has no effect upon the coagulation band, since a patient with lobar pneumonia and one with liver damage, both having the same icterus index, will have a short and a long coagulation band, respectively. Addition of bile or decholin to the serum in vitro has no effect upon the coagulation band.[1] The conclusion reached by most investigators has been that the reaction depends, in part at least, upon a qualitative change in the serum proteins, particularly the albumin, although the nature of this change is not known. Alterations in the electrolytes and the pH of the serum are reported to exert no demonstrable influence upon the reaction.[19, 21, 29, 56] Experiments performed in connection with the present study have been in accord with these findings. A more detailed analysis of the effect of chemical and physical agents upon the coagulation band will be presented in a separate report which outlines experimental work done on the serum coagulation reaction.

SUMMARY AND CONCLUSION

A brief review of the development and technique of performing the Weltmann serum coagulation reaction is presented. It is pointed out that the literature reveals no definite clue as to the physiochemical basis for the observed behavior of sera in different diseases. The exact nature of the phenomenon is not known.

The clinical application of the test, together with a compilation of the results of the test in a variety of diseases, has been made from the literature. The results of the Weltmann reaction performed on 246 unselected cases from the Pediatric Service of the University of Minnesota Hospital are shown to agree, in general, with the previously reported work. The clinical value of this laboratory test is discussed with special reference to its usefulness in diagnosis of early rheumatic fever and in following the progress of rheumatic fever. Similar emphasis is laid upon the possibility of its use in evaluating the element of infection in cases of acute abdominal pain in children, particularly in early appendicitis.

The author wishes to thank Dr. Irvine McQuarrie for valuable criticism during the course of these studies.

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AN EXPERIMENTAL STUDY OF THE WELTMANN SERUM COAGULATION REACTION

SUSAN COONS DEES, M.D.
MINNEAPOLIS, MINN.

THE Weltmann serum coagulation reaction was considered from a clinical point of view in another paper.[1] Its value as a simple laboratory test for aid in evaluating acute inflammatory and chronic fibrotic processes was stressed. Its usefulness in detecting liver damage in a variety of conditions was also mentioned. Despite fairly extensive investigation, the fundamental physicochemical or physiologic mechanism underlying the reaction still remains obscure. The present experimental studies were undertaken in an attempt to determine whether or not it could be modified or influenced by artificial means either in vivo or in vitro.

REVIEW OF LITERATURE

Weltmann suggested in his original work that the basis of the reaction consisted in alteration of the coagulation of serum albumin by heat in the presence of electrolytes.[2] However, he showed, by the similarity of results between 1:10, 1:50, and 1:100 dilutions of serum, that the albumin content of the solution tested is not the controlling factor. Frequently a 1:100 dilution had a longer band than a 1:50 dilution. As evidence that the ratios of the different serum proteins to each other, like the total proteins, have no relation to the length of the band, he cites results from two cases, one of pneumonia with a coagulation band of 0 and one of cirrhosis of the liver with a coagulation band of 9, both having an albumin-globulin ratio of 3/2. Fibrinogen would appear to play no significant role in the reaction, since serum and plasma give the same values. Furthermore, coagulation does not occur with fibrinogen solutions alone.[3] The role of globulin is less clear. Weltmann and Medvei[4] found a slight lengthening of the band when globulin was separated from the serum by dialysis, but when it was removed by precipitation with sodium chloride, the results were variable; either a lengthening or a shortening occurred. Kyriakis[5] states that globulin does affect the coagulation band. This is based upon the finding that the addition of precipitated globulin increases the amount of flocculum, while it has no effect upon

From the Departments of Pediatrics and Bacteriology, University of Minnesota.
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the length of the band. He found, also, that an albumin-fibrinogen mixture with globulin removed by precipitation was not capable of producing a true coagulation band. However, his fibrinogen-globulin mixture produced flocculation in all ten tubes, which again is not a true coagulation band. He concludes from these somewhat indecisive experiments that globulin increases the coagulation band, while albumin decreases it, and that changes in the coagulation band are dependent upon the amount of globulin and albumin present. Many others have determined the total proteins as well as the albumin-globulin ratio with respect to the coagulation band, and have found that neither has any direct relationship.[5, 6] In clinical conditions the relationship of the serum proteins to the length of the coagulation band is not striking.[7, 8] It is evident that a certain minimal amount of serum protein and electrolytes must be present in order to produce typical flocculation.[9] Of the serum electrolytes, calcium alone has been suggested as a possible factor. Kaiser[10] found that the coagulation band was prolonged by one tube fifteen minutes after intravenous administration of $CaCl_2$. He postulates that the increase in the coagulation band resulting from hemolysis may be due to the calcium liberated from the red blood cells. Weltmann,[2] Pongor,[11] and Kretz and Kudlac,[5] on the other hand, found no relationship between the values of the serum calcium and the length of the band. The addition of other electrolytes to the serum in vitro or in vivo had no effect upon the band.[4] Since the coagulation band is prolonged in some conditions in which jaundice occurs, it was thought that the presence of bile in the serum might influence the band. Weltmann[2] checked this by comparing the serum from a patient with pneumonia with that from a patient with cirrhosis, when both showed the same high icterus index. The band in the former was 0, while that from the patient with cirrhosis was 9. The addition of bile or decholin in vitro had no effect upon the coagulation band. Heparin added to serum in vitro shortens the coagulation band, according to Medvei and Paschkis.[12] The hydrogen ion concentration of the solution was found by Levinson and Klein[8] to have no effect upon the coagulation band. They believe that changes in blood pH may be correlated with lengthening or shortening of the band, but have no direct effect on it.[13]

Physical factors, such as aging,[14] freezing, irradiation, and inactivation at 56° C.,[4] have no effect upon the coagulation phenomenon. Substances which alter the colloidal state of the serum, such as adsorption on kaolin, seem to prolong and then to shorten the band, but gum arabic is without effect.[4] A summary of the effects of various physical and chemical agents upon the serum in relation to the coagulation band is shown in Table I which was compiled from the literature.

TABLE I

EFFECT OF VARIOUS PHYSICAL AND CHEMICAL FACTORS UPON THE COAGULATION BAND

METHOD OR SUBSTANCE USED TO TREAT SERUM	EFFECT	REFERENCE
Physical Agents		
1. Aging serum, 1 to 2 days	No effect	14
2. Sunshine	No effect	4
3. Irradiation	No effect	4
4. Freezing	No effect	4
5. Inactivation, 56° C.	No effect	4
6. Dilution to 1:100	No effect or slightly prolonged	2
7. Hemolysis of serum	Prolonged, 1-2	10
Chemical Agents		
1. Adsorption on kaolin	Prolonged, 1-2	4
2. Readsorption on kaolin	Shortened, 1-2	4
3. Gum arabic	No effect	4
4. pH of solutions	No effect	8
5. pH of serum	No effect	8
6. Bile	No effect	2
7. Decholin	No effect	2
8. Addition of Ba, Na, Mg	No effect	4
9. Calcium		
Ca in blood	No effect	11
Serum Ca	No effect	5
Ca intravenously	Prolonged	10
Addition of $CaCl_2$ to serum	No reaction	4
10. Amino acids		
Glycocoll	No effect	4
Asparagin	No effect	4
11. Lipids		
Cholesterol	No effect	4
Lecithin	No effect	4
12. Heparin	Shortened	12
13. Nonprotein nitrogen	No effect	3, 8
14. Serum proteins		
Total proteins	No effect	2, 5, 9
Albumin-globulin ratio	No effect	2, 4, 5, 6, 8, 15
Globulin removal	Slightly prolonged	4
Precipitated globulin	Prolonged or shortened	4
Addition of globulin	Increased flocculum; no change in band	8
Addition of albumin	No effect	3
Decrease in albumin	Shortened	3
Fibrinogen, serum, or plasma	No effect	2
Clinical Conditions		
1. State of hydration	No effect	4
2. Alkalinization	No effect	4, 8
3. Acidification	No effect	8, 25, 26
4. Fasting	No effect	4
5. Hyperpyrexia, induced	No effect	2, 27, 28
6. Thrombin content	No effect	29
7. Liver extirpation; Eck fistula	Prolonged	29
8. Portal obstruction	Shortened	29

METHODS AND MATERIALS

The standard technique for carrying out the Weltmann reaction[2] has been followed with two minor modifications. In order to reduce the amounts of reagent required, while maintaining the original 1:50 dilution of serum, half the usual quantities of calcium chloride solution and serum were used, 2.5 c.c. and 0.05 c.c., respectively. The stock

solution was made from $CaCl_2.2H_2O$. A 6.7 per cent solution of this salt is equivalent to the original 10 per cent solution of $CaCl_2.6H_2O$. During the course of the study, fresh stock solution and dilutions were made each week.

The Weltmann serum coagulation test is performed as follows: A series of ten dilutions of $CaCl_2.6H_2O$, ranging from 0.1 per cent to 0.01 per cent, is numbered from 1 to 10, beginning with the most concentrated. Two and one-half cubic centimeters of each dilution are measured into ten small test tubes. To each dilution is added 0.05 c.c. of fresh unhemolyzed serum. The tubes are thoroughly mixed, and immersed in a rack in a boiling water bath for fifteen minutes. At the end of this time, they are removed, and the highest dilution at which flocculation is present is noted. The normal band for human serum, as originally described by Weltmann and confirmed by others, consists of flocculation in the first six tubes, that is, through a dilution of 0.05 per cent calcium chloride. Pathologic sera show a striking shortening of the so-called coagulation band in acute infections and a lengthening of the band in chronic fibrotic conditions and in liver disease. In the experiments to be reported, several preliminary determinations of the band were done on normal rabbits and dogs, since there were no reported standards for these animals. The values in rabbits ranged from 5 to 6, and those in dogs were from 6 to 6½. Since much of the material from dogs was obtained as plasma, comparisons of plasma and serum were made. These gave identical coagulation bands.

MATERIALS

1. Stock solution, $CaCl_2.2H_2O$, 6.7 per cent.
2. Ten dilutions, 250 c.c. each, ranging from 0.1 per cent to 0.01 per cent $CaCl_2.6H_2O$.
3. Small test tubes (200).
4. Five wooden test tube racks.
5. Water bath at boiling temperature.
6. Volumetric flasks, one 100 c.c., and one 250 c.c.
7. Pipettes, one 10 c.c., graduated to 1/10 c.c., and ten 1 c.c., graduated to 1/100 c.c.
8. Unhemolyzed rabbit and human serum.
9. Twenty-three white male rabbits, weighing from 1,500 to 2,500 Gm., and nine black male rabbits, 2,200 to 2,800 Gm.
10. Chemicals:
    - Sodium ricinoleate (from the laboratory of Dr. W. P. Larson, Department of Bacteriology).
    - Calcium ricinoleate (1 per cent sodium ricinoleate, 5 c.c., plus 10 per cent $CaCl_2$, 1 c.c.)
    - Emulsified fat (Mead Johnson experimental product)
    - Oleic acid (Merck)
    - Palmitic acid (Merck)
    - Mineral oil (U.S.P.)
    - Acacia (Merck)
    - Kaolin

RESULTS

The experiments carried out were as follows:

1. A qualitative analysis of the chemical nature of the flocculum and clear supernatant fluid.

2. Determination of the role of proteins in the reaction.

3. Determination of the pH of the calcium chloride dilutions and of the serum-calcium chloride mixtures.

4. Studies on the role of calcium.

5. The relation of other blood electrolytes, especially in connection with induced hypoglycemia and anoxemia.

6. Experiments to show the effect of added colloids on serum coagulation.

7. Experiments with lipid substances, soaps, fats, and fatty acids.

An analysis of the coagulum obtained from pooled normal rabbit serum with a coagulation band of 5 was done by making a 1:50 dilution with 0.06 per cent calcium chloride and boiling for fifteen minutes. The supernatant fluid was removed by filtration. The coagulum was washed several times with distilled water and dried overnight at room temperature. It gave a positive Millon reaction and a positive biuret reaction. It was insoluble in dilute acid and alkali and 95 per cent alcohol, but soluble in concentrated HCl and saturated KOH. The filtrate gave negative Millon and biuret tests, and there was no precipitation after addition of 7 per cent trichloracetic acid. From these tests it was concluded that all of the protein had been removed from the mixture by flocculation, and that the coagulum obtained was largely protein in nature. Since the coagulum contains protein it seemed of interest to determine the minimum amount of protein necessary to produce a coagulation band. For this purpose, ascitic fluid containing 0.2 mg. per cent of protein, as determined by the osmotic pressure method, was used for a series of tests (Table II). The blood serum taken simultaneously gave a coagulation band of one. It has been shown by several observers that pleural exudates and transudates, ascitic and spinal fluids, usually have a coagulation band equal

TABLE II

COAGULATION BAND WITH ASCITIC FLUID

STRENGTH OF	1*	2	3	4	5	6	7	8	9	10
ASCITIC FLUID	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01
Undiluted	0‡	0	0	0	0	0	0	0	0	0
1:10	0	0	0	0	0	0	0	0	0	0
1:25	0	0	0	0	0	0	0	0	0	0
1:50	0	0	0	0	0	0	0	0	0	0

*Tube number.

†Percentage of $CaCl_2.6H_2O$.

‡0 = No turbidity or flocculation.

to or parallel to that of the blood serum taken at the same time.[6, 15] Pellegrini and Barsini[9] state that a certain minimum of albumin must be present, but that the total protein and ratio of the serum proteins have no effect upon the Weltmann reaction. From the experiment detailed above, using ascitic fluid, it would seem that a certain minimum of protein greater than 0.2 mg. per cent must be present in order to produce characteristic flocculation. Further studies seem to indicate that this minimum may be influenced by other factors.

The coagulation band was determined on the sera of a series of rabbits which were receiving large doses of horse serum in an attempt to produce serum sickness. In a few animals, the subcutaneous injection of foreign serum (from 7.5 to 10 c.c. per kilogram) was followed by a slight drop in the coagulation number on the seventh day, and again on the fifteenth day, three days after some of the animals had received a second injection of serum. In these animals the injection of large amounts of horse serum had no uniform effect upon the Weltmann reaction (Table III).

TABLE III

COAGULATION BAND AFTER SUBCUTANEOUS INJECTION OF HORSE SERUM

RABBIT	C.B.* BEFORE INJECTION	C. B. AFTER INJECTION OF HORSE SERUM		
		7 DAYS	15 DAYS	21 DAYS
7	6	2	5	5
8	6½	6½	5	-
11	5	3	4	5
12	5	3	3	5
13	5	4	3	5
14	5	5	4	4
15	1	(Died)	-	-
16	4	5	4	5
B_2	5	5	4	5

*C.B. = Coagulation band.

TABLE IV

pH OF CALCIUM CHLORIDE SOLUTIONS

SOLUTION	pH
0.1 % $CaCl_2.6H_2O$	5.25
0.07% $CaCl_2.6H_2O$	6.30
0.05% $CaCl_2.6H_2O$	5.75
0.01% $CaCl_2.6H_2O$	5.67

In an effort to learn whether the hydrogen ion concentration of the calcium chloride might be a significant factor in producing the coagulation band, pH determinations were done by the glass electrode method. That pH has no direct relationship to the concentration of calcium chloride is shown by some of the readings (Table IV). The pH of the calcium chloride-serum mixtures, both before and after boiling, was then determined colorimetrically by using a special "long-range indicator." The small amount of serum necessary to

produce a 1:50 dilution had sufficient buffer capacity to bring all of the tubes to the same pH. This pH was maintained after boiling fifteen minutes and after flocculation had occurred (Table V).

TABLE V

pH OF CALCIUM CHLORIDE SOLUTION PLUS SERUM 1:50, INDICATOR METHOD

SOLUTION $CaCl_2.6H_2O$ (%)	pH BEFORE BOILING	pH AFTER BOILING 15 MINUTES
0.1	7.2-7.4	7.2-7.4
0.09	7.2-7.4	7.2-7.4
0.08	7.2-7.4	7.2-7.4
0.07	7.2-7.4	7.2-7.4
0.06	7.2-7.4	7.2-7.4
0.05	7.2-7.4	7.2-7.4
0.04	7.2-7.4	7.2-7.4
0.03	7.2-7.4	7.2-7.4
0.02	7.2-7.4	7.2-7.4
0.01	7.2-7.4	7.2-7.4

N.B.: Method, 2.5 c.c. $CaCl_2.6H_2O$ solution + rabbit serum, .05 c.c. + "long-range indicator," 0.25 c.c. Coagulation band of serum = 5. The pH of the serum itself was not determined in relation to the length of or the production of the coagulation band since Levinson and Klein [8, 13] show that this is not a pertinent factor.

TABLE VI

EFFECT OF "DREFT" ON SERUM COAGULATION IN VITRO

SERUM	SERIES A (SERUM ALONE)		SERIES B (SERUM + 0.1 C.C. "DREFT")	
	C.B.	TURBIDITY	C.B.	TURBIDITY
Rabbit 7	0*	7	0	–
Rabbit 17	3	8	0	Faint opalescence (Tube 1)
Rabbit 18	4	8	0	Faint opalescence (Tube 1)
Human	1	7	0	Faint opalescence (Tube 1)

*Tube.

The role of calcium in the serum coagulation reaction was investigated in several experiments (Table VI). The calcium was removed from the reaction by addition of "Dreft," a sulfonated salt of fatty acids of high molecular weight. In one series the dilutions were set up in the usual fashion, and with the same sera a second series was made in which each tube also contained 0.1 c.c. of a 1 per cent solution of "Dreft." Four sera with different coagulation bands were chosen, and the number of tubes showing turbidity as well as flocculation in the control series was noted. In the series containing "Dreft," there was neither flocculation nor turbidity after boiling. Three sera showed the faintest opalescence in the first tube (0.1 per cent $CaCl_2.6H_2O$), the remainder being clear. It was necessary to add 1.2 c.c. of 10 per cent $CaCl_2$ to these tubes before even slight turbidity could be produced after boiling, and no flocculation whatsoever occurred. This is ten times the usual maximum amount of calcium which produces flocculation. Seven per cent trichloracetic acid was then added to the tubes of each series to determine qualitatively whether the proteins could still be precipitated. In Series A without "Dreft," in the tubes with coagulum no

precipitate occurred; in tube 10, however, in which there was no flocculation, protein was precipitated. In Series B with "Dreft," there was precipitate in all tubes after trichloracetic acid was added. The pH of all the tubes lay between 7.2 and 7.4. From this experiment one may conclude that available calcium is necessary to produce flocculation, and that the calcium must be present before the serum proteins are denatured by boiling. After boiling, relatively enormous amounts of calcium are necessary before even turbidity is produced, and no amount of calcium added at this time will produce flocculation.

The in vivo effect of "Dreft," was then studied. A marked drop in the coagulation band of a rabbit was noted forty-eight hours after the initial intraperitoneal injection of 5 c.c. of 1 per cent "Dreft." There was no reaction to the first injection, but the animal died in an anaphylactic-like shock within thirty minutes after the second injection was given two days later. Blood drawn immediately after onset of symptoms gave a coagulation band of zero. Since the chemical was obviously toxic, no other animals were injected. No definite conclusions can be drawn from only one observation, but the shortening of the coagulation band is striking in this one instance and suggests the possibility of a lowering of serum calcium as an explanation of the fall in the coagulation band.

TABLE VII

EFFECT OF INTRAVENOUS ADMINISTRATION OF CALCIUM CHLORIDE ON WELTMANN REACTION

RABBIT	C.B. BEFORE INJECTION	2 HOURS	18 HOURS
7	4	5	
17	0	4	
B_2	2	4	
11	3	5	5
14	0	0	0

The calcium effect was investigated from a different viewpoint by attempting to increase the blood calcium by intravenous injections. In the work of Collip[16] and Clark[17] on the effect of oral and hypodermic administration of calcium salts on the calcium content of rabbit blood, it has been shown that a slight transitory increase in calcium lasting up to from one and one-half to two hours can be produced by intravenous injection of calcium chloride. On the basis of these observations, five rabbits with short coagulation bands due to infection were injected intravenously with 5 c.c. of 10 per cent $CaCl_2$ and were bled at the end of two hours; two of the animals were bled again at the end of eighteen hours. Despite this initial short band, there seemed to be an increase in the coagulation band of from one to four tubes in all but one animal. In this rabbit the coagulation band was 0 on both determinations (Table VII). It might have been illuminating to extend the test

into the stronger dilutions as advocated by Kretz and Kudlac,[5] who differentiated subzero coagulation bands. It would seem that, for a short time after administration of calcium parenterally, the coagulation band is definitely increased in most animals. Kaiser[10] found that intravenous injection of calcium chloride increased the coagulation band slightly in human subjects. The negative results reported by certain observers[5, 11] after feeding calcium orally to patients without calcium deficiency hardly seem comparable in this instance, since it is apparently as difficult to increase the serum calcium in normal human subjects by this method as it is in experimental animals.

A series of determinations of the coagulation band were done on oxalated dog plasma obtained from experimental animals being used by Dr. Irvine McQuarrie and Dr. M. R. Ziegler in connection with studies on hypoglycemia and anoxemia. The coagulation band was found to bear no direct relationship to hemoconcentration, blood sugar, oxygen tension, or blood electrolytes. Since these experiments are now in progress and unpublished, the values for the above determinations will not be detailed.

Weltmann and Medvei[4] state that acacia had no effect upon serum coagulation. They also note that adsorption of kaolin prolonged the band, and readsorption then shortened it. They make no comment upon this observation, other than to say that they think the original adsorption removed some coagulation-preventing factor. The effect of these two very different colloids upon serum is an interesting one, and their behavior should throw some light on the serum-coagulating mechanism if it is related to a change in the colloidal states of the serum proteins.

The following experiments were carried out in vivo and in vitro, with gum acacia. A male rabbit weighing 2.15 kg. was given a series of three injections of 6 per cent gum acacia, 20 c.c. intravenously. The second injection was given after a two-day interval, and the third one, on the fifth day. The animal was bled two hours after the first injection, four hours after the second, and eight hours after the third. There was no reaction to the injections, and the animal gained 90 Gm. in weight in a five-day period. The results of this experiment are shown in Table VIII. There was a very slight increase in the coagulation band two hours after the first injection of acacia. This was not maintained for forty-eight hours. Four hours after the second injection there was also an increase of one tube in the coagulation band, and a further increase of 1½ tubes forty-eight hours after this injection. However, eight hours after the third injection on the fifth day of the experiment, the coagulation band dropped slightly. These results show that acacia has no striking effect upon the coagulation band when given intravenously, but they suggest that temporary increase may be produced within a four-hour period.

TABLE VIII

COAGULATION BAND AFTER INJECTION OF GUM ACACIA SOLUTION (6 PER CENT)

RABBIT 7	1*	2	3	4	5	6	7	8	9	10	COAGULATION BAND
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Normal serum	++++	++++	++++	-	-	-	-	-	-	-	3
Injection I											
2 hr.	++++	++++	++++	++	-	-	-	-	-	-	3½
48 hr.	++++	++++	-	-	-	-	-	-	-	-	2
Injection II											
4 hr.	++++	++++	++++	-	-	-	-	-	-	-	3
48 hr.	++++	++++	++++	++++	++	-	-	-	-	-	4½
Injection III											
8 hr.	++++	++++	++++	++++	-	-	-	-	-	-	4

*Tube number.
†Percentage of $CaCl_2.6H_2O$.

TABLE IX

COAGULATION BAND AFTER ADDITION OF 6 PER CENT GUM ACACIA SOLUTION

	1*	2	3	4	5	6	7	8	9	10	COAGULATION BAND
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Human serum	++	++	++	++	++	++	++	-	-	-	7
With acacia	++	++	++	++	++	++	++	-	-	-	7
Rabbit serum	++	++	-	-	-	-	-	-	-	-	2
With acacia	++	++	++	++	-	-	-	-	-	-	4
Acacia, 0.1 c.c.	0	0	0	0	0	0	0	0	0	0	No band

*Tube number.
†Percentage of $CaCl_2.6H_2O$.

Addition of 0.1 c.c. of 6 per cent acacia to serum with a relatively long band was without effect in vitro, although the same amount increased a short band by two tubes (Table IX).

The effect of adsorption of kaolin was studied on several sera and on ascitic fluid. Weltmann's results of a definitely prolonged band were confirmed in the original adsorption, but readsorption failed to reduce the band as in his experiments (Table X).

The possible relationship between the lipid constituents of the serum and heat coagulation has received little attention by previous investigators. Weltmann and Medvei[4] state that the addition of cholesterol and lecithin has no effect upon the band, but no further details are given. Levinson and Klein[5] included determinations of blood cholesterol on several patients and found no correlation with the length of the coagulation band. Experiments were carried out, using sodium ricinoleate, calcium ricinoleate, oleic acid, palmitic acid, olive oil, mineral oil, and neutral emulsified fat. These substances were used for intraperitoneal injection into rabbits and for in vitro studies on rabbit and human serum.

TABLE X

COAGULATION BAND AFTER ADSORPTION OF KAOLIN

	1*	2	3	4	5	6	7	8	9	10	COAGULATION BAND
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Human I	++	++	++	-	-	-	-	-	-	-	3
With kaolin	++	++	++	++	++	++	-	-	-	-	6
Readsorption	++	++	++	++	++	++	-	-	-	-	6
Human II	++	++	++	++	-	-	-	-	-	-	4
With kaolin	++	++	++	++	++	++	++	+	-	-	7½
Readsorption	++	++	++	++	++	++	++	+	-	-	7½
Human III	++	++	++	++	+	-	-	-	-	-	4½
With kaolin	++	++	++	++	++	++	++	+	-	-	7½
Readsorption	++	++	++	++	++	++	++	+	-	-	7½
Ascitic fluid	0	0	0	0	0	0	0	0	0	0	No band
With kaolin	0	0	0	0	0	0	0	0	0	0	No band
Readsorption	0	0	0	0	0	0	0	0	0	0	No band

*Tube number.
†Percentage of $CaCl_2.6H_2O$.

Sodium Ricinoleate.—The coagulation band was determined in four groups of rabbits after intraperitoneal injection of 1 per cent sodium ricinoleate. The amounts of the chemical injected varied from 2 to 6 c.c. per kilogram of body weight. The animals were bled fifteen minutes, forty-five minutes, one and one-half hours, three hours, eight hours, and thirty-two hours following injection. In series III and IV, blood was

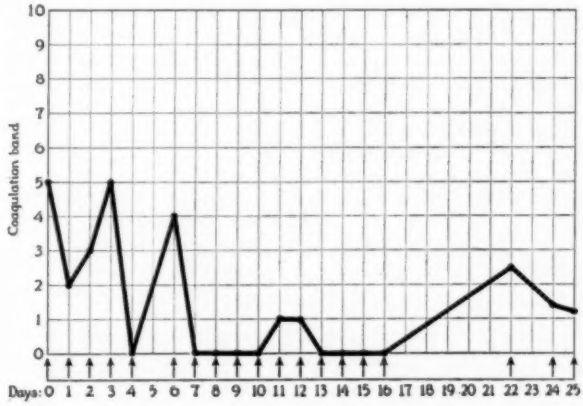

Fig. 1.—Effect of intraperitoneal injection of sodium ricinoleate upon coagulation band.

taken only at eight and thirty-two hours, since previous experiments indicated that little or no change occurred in a shorter time. In these animals a definite shortening of the coagulation band took place eight hours after injection of from 2 to 6 c.c. of 1 per cent sodium ricinoleate per kilogram of body weight. This shortened band is still present in

most cases at thirty-two hours. The results of this experiment are shown in Table XI.

In order to determine whether or not this fall in the coagulation band could be maintained for a long period of time, daily intraperitoneal injections of 4 c.c. of 1 per cent sodium ricinoleate were given. In one experiment, a rabbit weighing 2.09 kg. was bled and injected over a period of twenty-five days. A sharp fall in the coagulation band was observed after the sixth day of injection (Fig. 1).

TABLE XI

EFFECT OF SODIUM RICINOLEATE UPON COAGULATION BAND IN VIVO

RABBIT	WEIGHT (GM.)	SODIUM RICINOLEATE 1 PER CENT	COAGULATION BAND			
Series I						
			BEFORE INJECTION	15 MIN.	45 MIN.	1½ HR.
11	2,270	4 c.c./kg. = 9 c.c.	5	5	5	5
12	2,155	4 c.c./kg. = 8.5 c.c.	5	4	5	5
13	1,645	3 c.c./kg. = 5 c.c.	5	5	5	5
14	2,245	Control	5	5	5	5
Series II						
			BEFORE INJECTION	3 HR.	8 HR.	32 HR.
7	2,010	4 c.c./kg. = 8 c.c.	5	6	0	0
17	1,562	6 c.c./kg. = 8 c.c.	4	6	2	0
B_2	2,710	5 c.c./kg. = 13 c.c.	5	7	6	4
Series III						
			BEFORE INJECTION		8 HR.	32 HR.
7	1,787	3 c.c./kg. = 5 c.c.	5½		4	4
17	1,530	3.3 c.c./kg. = 5 c.c.	3		2	0
B_2	2,570	2 c.c./kg. = 5 c.c.	6		4	2
Series IV						
			BEFORE INJECTION		8 HR.	32 HR.
7	1,737	3 c.c./kg. = 5 c.c.	6		5	5
17	1,455	3.5 c.c./kg. = 5 c.c.	6		4	5
B_2	2,455	Control	6		6	6

In Vitro Experiments.—The coagulation band was determined on several rabbit and human sera alone and after the addition of 1 per cent sodium ricinoleate. In all of the sera tested there was a striking fall in the coagulation band as is shown in Table XII.

Calcium Ricinoleate.—The calcium salt was made by adding 1 c.c. of 10 per cent $CaCl_2$ to 5 c.c. of 1 per cent sodium ricinoleate. Rabbits were injected intraperitoneally at forty-eight-hour intervals with this material. Fig. 2 shows the effect upon the coagulation band in one rabbit which received a series of three injections at forty-eight-hour intervals. While it was expected that a definite prolongation would

TABLE XII

EFFECT OF SODIUM RICINOLEATE UPON COAGULATION BAND IN VITRO

SERUM	C.B.	C.B. AFTER ADDITION OF 0.1 C.C. 1 PER CENT SODIUM RICINOLEATE
Series I		
Human L.	4	2
Human S.	4½	3
Rabbit 7	5½	1
Rabbit 17	3	1
Rabbit B_2	6	0
Rabbit B_3	4	1½
Series II		
Rabbit 7	6	0
Rabbit 17	6	0
Rabbit B_2	6	1
Human I	5	2
Human II	4	2
Human III	8*	7½†

N.B.: Human serum III obtained from patient with lipoid distrophy with extreme lipemia.

*All tubes showed clear supernatant fluid, bulky coagulum.

†All tubes showed cloudy supernatant fluid, very scant coagulum.

be produced, only a very slight increase in the coagulation band was observed after the first and third injections. The animals used to illustrate this effect had received a series of injections of sodium ricinoleate two weeks previously.

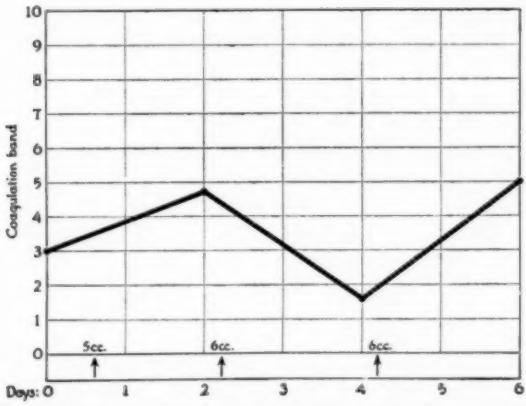

Fig. 2.—Effect of intraperitoneal injection of calcium ricinoleate upon coagulation band.

Emulsified Fat.—The effect of fat upon the coagulation band was studied by the intravenous injection into rabbits of 5 c.c. of a highly emulsified fat prepared for clinical use. In three animals so treated there was no increase in the coagulation band in fifteen minutes, three hours, and eighteen hours. However, when one drop of this fat was added to each dilution of calcium chloride and serum, the band was

definitely prolonged. The fat alone produced no turbidity or flocculation in the control tubes of calcium chloride. Mineral oil had no effect upon the band (Table XIII).

TABLE XIII

EFFECT OF FAT UPON COAGULATION BAND IN VITRO

SERUM	COAGULATION BAND (SERUM ALONE)	COAGULATION BAND (WITH FAT)*	COAGULATION BAND (WITH MINERAL OIL)†
Human A	7	8	7
Human D	6	9	6
Rabbit 7	5	8	5
Rabbit B	5	9	5
Control, fat 1:50	--		
Mineral oil 1:50	--		

*Neutral fat, 1 drop in each tube.
†Mineral oil, 1 drop in each tube.

Oleic Acid and Palmitic Acid.—Oleic acid and palmitic acid were added to the serum dilutions in minimal quantities (one drop in each tube), and a most striking prolongation of the coagulation band resulted, as is shown in the accompanying tables. In most instances the band was prolonged to 9 or 10, regardless of the original range of flocculation. In addition, the amount of coagulum was increased, and the supernatant fluid was almost always perfectly clear. When the supernatant fluid was tested with 7 per cent trichloracetic acid, there was no cloudiness, showing that all of the protein had been coagulated. This coagulation occurred only after boiling, and it was not extensive when the fatty acid was not well emulsified by shaking. When fatty acid was added to a series of tubes which had been treated in the usual fashion by boiling for fifteen minutes, there was immediate clearing of the supernatant fluid in the tubes containing floceulum. If the series was then boiled for an additional two to five minutes, the coagulation band was widened by several tubes. Ascitic fluid containing 0.2 mg. per cent of protein and having no coagulation band whatsoever, on treatment by saturation with palmitic acid, developed typical coagulation in the first two tubes. These findings are shown in Tables XIV and XV.

A comparison of the effect of olive oil and oleic acid showed that a similar but less marked increase could be produced by the oil. This is shown in Table XVI.

To check the possibility of the coagulation being due solely to an increase in acidity, the pH was determined colorimetrically before boiling and at the boiling point. This was found to lie between pH 7.2 and pH 7.4 in all the sera treated with fatty acids. After coagulation had occurred, the pH in the tubes containing fatty acid occasionally fell to pH 5. Because this drop in pH developed after flocculation, it was thought that increase in acidity might still play a part in the prolongation of the coagulation band on addition of fatty acids. For this reason, a group of ten sera was treated with various concentrated acids;

TABLE XIV

EFFECT OF FATTY ACID UPON COAGULATION BAND IN VITRO

SERIES I. MIXTURE BEFORE BOILING

SERUM	1*	2	3	4	5	6	7	8	9	10	C.B.
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Human B	++++	++++	++++	++++	++++	++++	++++	–	–	–	7
With oleic acid[1]	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human I	++++	++++	++++	++++	–	–	–	–	–	–	4
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human II	++++	++++	++++	++++	++	–	–	–	–	–	4½
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human III	++++	++++	–	–	–	–	–	–	–	–	2
With oleic acid[2]	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Human V. H.	–	–	–	–	–	–	–	–	–	–	0
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Dog 1[3]	++++	++++	++++	++++	–	–	–	–	–	–	4
With palmitic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Ascitic fluid	0	0	0	0	0	0	0	0	0	0	No band
With palmitic acid	++++	++++	–	–	–	–	–	–	–	–	2

*Tube number.

†Percentage of $CaCl_2.6H_2O$.

[1]Oleic acid, 0.1 c.c. in each tube.

[2]Oleic acid, 1 drop in each tube.

[3]Palmitic acid, saturated solution.

TABLE XV

EFFECT OF FATTY ACID ON COAGULATION BAND IN VITRO

SERIES II. MIXTURE AFTER BOILING (REHEATED 2-5 MINUTES)

SERUM	1*	2	3	4	5	6	7	8	9	10	C.B.
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Human G. F.	++++	++++	++++	++++	++++	++++	–	–	–	–	6
With oleic acid[1]	++++	++++	++++	++++	++++	++++	++++	++++	++++	+	9
Human B. R.	++++	++++	++++	++++	++	–	–	–	–	–	4½
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Human C. D.	++++	++++	++++	++++	–	–	–	–	–	–	4
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human R. T.	++++	++++	++++	++	–	–	–	–	–	–	3½
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human D. S.	++++	++++	++++	–	–	–	–	–	–	–	3
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	10
Human M. G.	++++	++++	++++	++	–	–	–	–	–	–	3½[2]
With oleic acid	++++	++++	++++	++++	–	–	–	–	–	–	4
Human M. M.	–	–	–	–	–	–	–	–	–	–	0[2]
With oleic acid	++++	++++	++++	–	–	–	–	–	–	–	3
Human M. C.	++++	++++	++++	++++	++++	–	–	–	–	–	5
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	–	–	8
Human 12	++++	++++	++++	++++	++++	–	–	–	–	–	5
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Human 13	++++	++++	++++	++++	–	–	–	–	–	–	4
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Rabbit 7	++++	++++	++++	++++	++++	++++	–	–	–	–	6
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	–	–	8
Rabbit 17	++++	++++	++++	++++	++++	++++	–	–	–	–	6
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Rabbit B_2	++++	++++	++++	++++	++++	++++	–	–	–	–	6
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9

*Tube number.

†Percentage of $CaCl_2.6H_2O$.

[1]Oleic acid, 1 drop in each tube.

[2]Tubes not shaken after addition of fatty acid.

TABLE XVI

COMPARISON OF EFFECT OF OLIVE OIL AND OLEIC ACID UPON COAGULATION BAND IN VITRO

SERUM	1*	2	3	4	5	6	7	8	9	10	C.B.
	0.1†	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	
Human 12	++++	++++	–	–	–	–	–	–	–	–	2
With olive oil	++++	++++	++++	++++	++++	++	–	–	–	–	5½
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9
Human V. H.	–	–	–	–	–	–	–	–	–	–	0
With olive oil	++++	++++	++++	++	–	–	–	–	–	–	3½
With oleic acid	++++	++++	++++	++++	++++	++++	++++	++++	++++	–	9

*Tube number.

†Percentage of $CaCl_2.6H_2O$.

N.B.: Olive oil and oleic acid, 1 drop in each tube.

the resulting pH was less than pH 5 in all cases, and in none was there any change in the coagulation band after the addition of acid. It would seem from this experiment that the effect of the fatty acid in prolonging the coagulation band is a property peculiar to its lipid, rather than its acid, character (Table XVII).

TABLE XVII

EFFECT OF ACIDS UPON COAGULATION BAND IN VITRO

SERUM	C.B. SERUM ALONE	C. B. WITH		
		BORIC ACID	TRICHLORACETIC ACID	HCl
Human C. D.	4	4	4	4
Human C. P.	4	4	4	4
Human R. T.	3½	3½	3½	3½
Human D. S.	3	3	3	3
Human M. G.	3½	3½	3½	3½
Human M. M.	0	0	0	0
Human M. C.	5	5	5	5
Rabbit 7	6	6	6	6
Rabbit 17	6	6	6	6
Rabbit B_2	6	6	6	6

N.B.: Boric acid, saturated solution, 0.1 c.c. in each tube. Trichloracetic acid, 20 per cent, 0.1 c.c. in each tube. HCl, concentrated, 1 drop in each tube.

DISCUSSION

Slight alterations in the Weltmann serum coagulation reaction can be produced by increasing or decreasing the amount of calcium available for the reaction. Since the test is based upon the coagulation of serum proteins by heat in the presence of an electrolyte, namely calcium, this is to be expected. That serum calcium does not play an all-important role is shown by the experiments presented and by clinical conditions in which there are alterations in blood calcium with no change in the coagulation band.

The most striking effect upon the band was produced by two quite different substances, kaolin and fatty acids. Both of these lengthened the range of coagulation greatly. These two chemicals have the common property of altering the colloidal state of substances with which they are mixed in that they decrease surface tension and increase particle size. Further studies to determine whether there is an actual relation between the molecular size of serum proteins and surface tension of the serum in producing the Weltmann reaction will be carried out.

That blood fatty acids are reduced in acute infectious states has been shown by Stoesser and McQuarrie,[20] and by Stoesser.[21-23] The coagulation band is uniformly reduced in such conditions. In anemia, leucemia, nephritis, and diabetes, the blood fatty acids are increased.[24] These conditions have a prolonged coagulation band. In liver diseases in which the coagulation band is almost always prolonged, there is a disturbance in the lipoid metabolism, usually involving the desaturation of fatty acids.[24] It has been shown experimentally that the addition

of fatty acids to serum in vitro will increase the coagulation band. It is suggested by these observations that, in clinical conditions, the level of blood fatty acids and the amount of unsaturation may be factors which greatly influence the length of the coagulation band. Unfortunately, values for blood fatty acids are not available for all of the diseases in which the Weltmann reaction has been used.

SUMMARY AND CONCLUSIONS

1. The literature pertaining to the experimental aspects of the Weltmann serum coagulation reaction is briefly reviewed. The effects of serum proteins, electrolytes, pH, bile, and various physical agents are presented in tabular form.

2. The technique and materials necessary for performing the Weltmann reaction are outlined in detail.

3. Original experiments are described in which an attempt was made to alter the Weltmann reaction by various chemical agents, both in vivo and in vitro. These experiments also included pH determinations on serum electrolyte mixtures and a qualitative analysis of the coagulum produced by the reaction. The substances studied were serum proteins, calcium, mineral and organic acids, acacia, kaolin, and lipids. The lipids included sodium ricinoleate, oleic and palmitic acids, olive oil, mineral oil, and an emulsified neutral fat.

4. It was found that the coagulum is protein in nature and that an amount of protein greater than 0.2 mg. per cent is necessary for the production of flocculum.

5. The pH of serum or of a serum-calcium chloride mixture has no effect upon or relationship to the reaction.

6. The injection of foreign serum has no uniform effect upon the coagulation band.

7. Calcium is an essential for the coagulation reaction. This is shown by the failure of coagulation to occur when calcium is removed from the system by the addition of a sulfonated fatty acid which has a marked affinity for calcium. Calcium injected intravenously tends to prolong the coagulation band for a short time.

8. Electrolytes other than calcium and the physiologic states of hypoglycemia and anoxemia have no effect upon the reaction.

9. The colloid, acacia, injected intravenously, prolongs the coagulation band slightly for four hours. Addition of acacia lengthens a short band.

10. Adsorption of serum on kaolin lengthens the coagulation band. Readsorption does not effect any further change.

11. Sodium ricinoleate produces a shortening of the band in vitro and in vivo. Oleic and palmitic acids greatly lengthen the coagulation band in vitro. Olive oil produces a similar, but less marked, effect.

The increase in the coagulation band upon addition of fatty acids is not due to increase in acidity, since other organic acids and mineral acids do not affect the band.

12. Attention is drawn to the short band in acute infectious states in which the blood fatty acids are low, and to the long band in anemia, leucemia, nephritis, and diabetes, in which there is an elevation of blood fatty acids.

13. It is suggested that the serum lipids are a decisive factor in determining the length of the coagulation band.

The author wishes to thank Dr. Irvine McQuarrie and Dr. W. P. Larson for valuable criticism during the course of these studies.

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PREVENTION OF RICKETS IN PREMATURE INFANTS WITH PARENTERAL ADMINISTRATION OF SINGLE MASSIVE DOSES OF VITAMIN D

CARL ZELSON, M.D.
NEW YORK, N. Y.

THE study of prophylaxis of rickets can be best carried on in premature infants. Rickets develops in every premature infant unless adequate preventive measures are taken, and frequently even in spite of such measures. Due to intensity of growth, lack of adequate calcium and vitamin D reserves, and inability to absorb fat, rickets appears early, progresses rapidly, and assumes severe degrees in premature babies. This occurs particularly in infants with low birth weight. The inability to utilize fat probably impairs the absorption of vitamin D from the intestinal tract.[1] This may explain why oral vitamin D prophylaxis often fails and larger amounts of vitamin D are required than in infants born at term. In this respect, the premature infant resembles the child with celiac disease.

Insufficient absorption of orally administered vitamin D is only one of the reasons for the superiority of the parenteral vitamin D shock prophylaxis in premature infants. Other reasons, which apply to full-term as well as premature infants, have been outlined by Vollmer[2b] in a previous publication which also presents the general principles of parenteral administration of massive doses of vitamin D.

This study had the great advantage of an unusually large number of premature infants treated in the Harlem Hospital. However, the results which are presented at this time are somewhat incomplete because of the fact that we were unable to follow all of our cases adequately.

Forty-six premature infants received single massive doses of various vitamin D preparations. A single dose of 600,000 units of crystalline vitamin D_2* or D_3† in 0.7 c.c. of peanut oil and 0.3 c.c. of ether was administered parenterally to twenty infants. The others received a single dose of from 200,000 to 500,000 units of another preparation‡ by mouth.

From the Pediatric Service of Harlem Hospital, New York, Dr. Morris Gleich, Director.

The work presented here is a continuation of the studies previously presented by Vollmer [2a and b] on the administration of single massive doses of vitamin D. He suggested this problem and helped in the compilation of the paper.

*Calciferol, Burroughs Wellcome Co.

†Alba Pharmaceutical Company.

‡Ertron, Nutrition Research Laboratory, Chicago, Ill.

None of the forty-six premature infants showed any clinical signs of toxicity or calcium-containing casts in the urine following the administration of these massive doses of vitamin D. Local infiltrations at the site of the intramuscular injection of vitamin D did not occur.

TABLE I

CASE NO.	BIRTH WEIGHT (LB., OZ.)	AGE IN DAYS AT THE TIME OF VITAMIN D ADMINISTRATION	FOLLOW-UP SYMPTOMS FOR RICKETS						
			AGE IN DAYS	CLINICAL SYMPTOMS	AGE IN DAYS	ROENTGENOGRAPHIC SYMPTOMS	CHEMICAL SYMPTOMS		
							AGE IN DAYS	CALCIUM (MG. %)	PHOSPHORUS (MG. %)
Parenteral									
1	2, 11	33	85	None	85	None	146	10.8	7.0
			146	None					
2	3, 9	18	31	None	31	None	18	9.9	7.6
							32	13.7	6.3
							51	11.2	–
							109	11.5	8.9
3	3, 12	19	55	None	55	None	95	11.1	6.5
			95	None					
4	4, 8	20	56	None	56	None	61	10.9	5.6
5	4, 8	23	85	None	85	None	85	9.8	6.2
			113	None			113	11.0	6.3
6	4, 10	20	53	None	53	None	75	11.8	6.4
			75	None					
7	4, 11	25	279	None	279	None		–	–
8	4, 12	16	47	None		–	47	12.7	6.7
9	4, 13	22	75	None	75	None	89	10.8	7.4
10	4, 14	14	32	None	32	None	32	12.0	7.4
			51	None			51	10.5	7.0
11	5, 0	14	44	None	44	None	58	10.7	5.3
			58	None					
Oral									
12	3, 8	21 (500,000)	99	Craniotabes	94	Hypoplastic rickets	98	9.7	4.1
		99 (600,000)					101	9.6	5.3
							109	10.0	4.5
			111	Healing craniotabes	111	Healing rickets	113	10.1	5.7
							127	10.3	4.9
							141	11.1	7.6
			262	None					
13	3, 12	25	57	None	57	None	83	10.9	6.5
			83	None					
14	3, 15	18	58	None	58	None	49	9.8	7.4
15	3, 15	25	64	None	64	None	64	10.9	6.2
16	4, 6	15	44	None	30	None	30	11.0	8.2
							44	11.3	6.8
17	4, 14	12	44	None		–	44	11.5	5.1

Only seventeen infants of this group could be studied for the planned length of time. The others, after discharge from the hospital, did not return at all or could be followed only for a short period. The seventeen infants are listed in Table I. Their birth weights ranged between 2 pounds 11 ounces and 5 pounds. The preventive single dose of vitamin D was administered between the twelfth and thirty-third days of life (during the winter of 1938-1939). Cases 1 to 11 received one dose of

600,000 units of vitamin D_2 or D_3 parenterally; Cases 12 to 17 were given 500,000 units of an oral vitamin D preparation.* After this prophylactic dose, no other vitamin D preparation or ultraviolet irradiation was given either in the hospital or at home until we directed it to be done.

Rickets appeared in only one premature infant, Case 12. This was a female colored child who weighed 3 pounds 8 ounces at birth and received 500,000 units of vitamin D by mouth at the age of 3 weeks. At the beginning of the fourth month, there was definite craniotabes. The x-ray of the wrist showed hypoplastic rickets, and the serum calcium was 9.7; the phosphorus was 4.1 mg. per cent.† When this child was 99 days old, she received a second dose of 600,000 units of vitamin D_2 by mouth. Twelve days later, the craniotabes had improved considerably. X-ray examination showed healing rickets. Fourteen days after this second administration of vitamin D, the serum calcium was 10.1, and the phosphorus 5.7, mg. per cent. The calcium and phosphorus remained normal up to the one hundred and forty-first day, when they were 11.1 and 7.4 mg. per cent, respectively. The physical examination on the two hundred and sixty-second day of life revealed no clinical signs of rickets.† The inability of 500,000 units of the oral vitamin D preparation to prevent rickets in this case is quite significant. The oral administration at an age when vitamin D absorption is still inadequate is probably the main reason for the failure. The subsequent second oral administration of 600,000 units of vitamin D_2 cured the rickets which had appeared, and prevented further relapses for a considerable length of time. This different response to the second dose can be sufficiently explained by the more advanced age and the consequently improved vitamin D absorption. A second reason for the failure of the oral preparation to prevent rickets might also be considered. The substance we used is ergosterol activated by fast electrons and probably ions. It is available in capsules containing a mixture of activated and inactivated ergosterol. Neither nitrogen nor proper solvent is proved to prevent oxidation and subsequent loss of potency. It is possible that this preparation, when used sometime after the activation process, possesses considerably less antirachitic efficacy than when originally assayed. This has been confirmed by spectroscopic analysis.[8]

The other sixteen premature infants did not show any clinical, roentgenographic, or chemical signs of rickets up to the time of the last examination. The periods of observation, however, varied considerably. Therefore, no definite conclusion is justified as to the minimum period of complete protection by one massive dose of vitamin D. Nevertheless, it seems reasonable to assume from the available evidence that rickets in

*Ertron, Nutrition Research Laboratory, Chicago, Ill.
†Data obtained in the Babies Hospital.

premature infants can be prevented for three months by the parenteral administration, although not necessarily by the oral administration, of one single dose of 600,000 units of vitamin D.

COMMENT

Successful efforts to prevent rickets in rats by one single massive dose of vitamin D, amounting to about one thousand times the effective single daily dose, have been reported by Vollmer as early as 1928.[3] These experiments proved that rats are capable of retaining from a single massive dose administered orally or parenterally as much vitamin D as is necessary for the prevention of rickets.

Ten years later, with purer and safer vitamin D preparations, similar clinical attempts were made by several investigators in cases of infants born at term. All these reports refer to the oral administration of single massive doses of vitamin D. Brockmann[4] followed sixty out of one hundred infants who had received one single prophylactic dose of 600,000 units (15 mg.) of vitamin D_2 or D_3. He found that this dose given in winter suffices to prevent rickets for not more than three to four months in healthy infants. He advocated that, in order to secure full protection, two such prophylactic doses be given, one in October and the second at the end of January. Harnapp[5] observed seventy-one children between 2 months and 1½ years of age. One prophylactic dose of 5, 7.5, or 10 mg. (200,000, 300,000, or 400,000 units) of vitamin D_2 or D_3 was administered orally in December, and the children were followed up to the middle of February. Only one of the children, who had received 5 mg. of vitamin D, developed rickets. The observation period, however, was short, as it did not exceed ten weeks.

Five premature infants (twins and triplets) were included in the series of Brockmann.[4] They received the preventive dose at an age exceeding 2½ months; their body weight exceeded 3,500 Gm. As to their vitamin D requirement and their ability to absorb vitamin D, these children were likely to resemble infants born at term rather than those born prematurely.

Harnapp[5] found 200,000 units of vitamin D insufficient, but regarded from 300,000 to 400,000 units as an adequate dose for the prevention of rickets. The short observation periods of Harnapp, as well as the higher age of his children, do not permit the conclusion that his prophylactic doses represent the optimum. The dose of 600,000 units as used by Brockmann may appear rather arbitrary. Nevertheless, this larger dose will most likely give better results and cover, to a greater extent, the requirement which varies with the individual patient. Moreover, it appears to be better adapted to the generally higher requirement of premature infants.

If we may assume that 600,000 units of vitamin D would prevent rickets for one hundred days, and that on the average, 93 per cent of

this massive dose would be absorbed and retained by the infants, as Windorfer stated,[6] approximately 6,000 units of vitamin D per day would be consumed for the prevention of rickets. This is certainly a large dose and might be the requirement for some premature infants, but, by no means, for babies born at term. Newborn infants require between 1,000 and 1,500 units daily for the prevention of rickets. Therefore, the conclusions of Windorfer appear disputable. Windorfer[6] found by a colorimetric method that only from 3.17 to 14 per cent of the massive vitamin dose administered by mouth is recoverable in the stool. Two errors are conceivable: Either the colorimetric method is not reliable, or the molecule of vitamin D in part undergoes chemical changes on its way through the intestinal tract and reappears in the stool in a form different from vitamin D. Determinations of the vitamin D content in various organs of three children by Vollmer[7] did not confirm Windorfer's optimistic conception as to the retention and storage of vitamin D administered in massive doses.

The advantages of the parenteral method of vitamin D shock prophylaxis over the oral method are obvious:

1. Single manipulation controlled by the physician.

2. Guarantee that a precise quantity of vitamin D is incorporated and retained.

3. Freedom from the variations of the mother's care.

4. Avoidance of differences in absorption of vitamin D from the gastrointestinal tract.

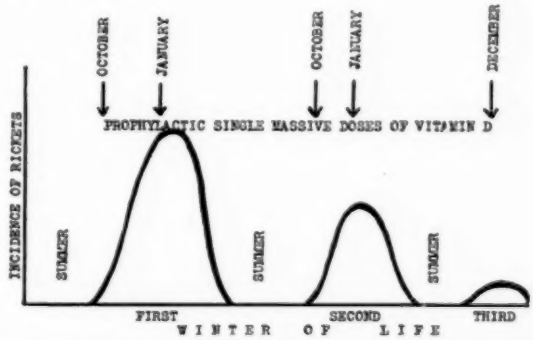

Fig. 1.—Schematic illustration of the incidence of rickets and vitamin D shock prophylaxis during the first three years of life. (By Vollmer.)

How frequently are the prophylactic doses to be given? The definite need probably varies with the individual child, depending upon term and season of birth, race, constitution, diet, social factors, and geographic and climatic conditions. As with the routine prophylaxis, using continuous small doses, an excess of vitamin D is usually given; so, here, too, to be on the safe side, the dose given must be adapted to infants most

inclined to rickets even though this might be an excess of vitamin D for the children who are less inclined to rickets. Premature infants need the first dose very early, approximately in the third week of life. It should be repeated three months later. Subsequently, premature infants resemble infants born at term in their vitamin D requirement.

As illustrated in Fig. 1, the highest incidence of rickets occurs in the first winter of life, when the vitamins stored during the preceding summer are exhausted and the infant is still growing at a high rate. At this period of life, many children will be completely protected by one single massive dose of vitamin D in the middle of the winter. In order to secure complete protection for every individual child, two doses, one in October and one in January, are generally advocated. This procedure is repeated in the second winter of life, despite the fact that there is a lower incidence of rickets. In the third winter, rickets occurs relatively rarely; one single preventive dose in December might suffice.

Fig. 1 (as suggested by Vollmer) presents merely a proposition for studies of vitamin D shock prophylaxis. Further experience over a period of years will be required to decide whether or not this plan can be improved or modified.

SUMMARY

Parenteral and oral vitamin D shock prophylaxis was carried out in forty-six premature infants. Only seventeen of them could be followed up to an age of from 44 to 279 days. During these periods, no rickets appeared in the premature infants who received 600,000 units of vitamin D_2 or D_3 parenterally.

One premature infant who received 500,000 units of an oral vitamin D preparation on the twenty-first day of life showed rickets at the beginning of the fourth month. A second oral dose of 600,000 units of vitamin D_2 cured and prevented rickets up to the two hundred and sixty-second day of life.

A plan, as suggested by Vollmer, for the general prevention of rickets with parenteral vitamin D shock prophylaxis is also presented.

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498 WEST END AVENUE

THE USE OF A SOYBEAN EMULSION IN A SIMPLIFIED REGIME FOR THE STUDY AND TREATMENT OF INFANTILE ECZEMA

SAMUEL J. LEVIN, M.D.
DETROIT, MICH.

THE recent excellent reviews on the subject of infantile eczema, among others those by Hill[1, 2] and Rappaport and Hecht,[3] are very comprehensive and exceedingly helpful to an understanding of this difficult subject. The importance of very careful history taking and subsequent study by means of skin testing, environmental control, and trial diets has been emphasized sufficiently not to require repetition here. The purpose of this paper is to outline a simplified method in the study and treatment of infantile eczema, which has been evolved over a period of three years in the study of eighty-six cases. These patients have been seen both in the outpatient clinic and in private practice. One of the chief difficulties in the handling of infantile eczema is the need of a satisfactory milk substitute. Evaporated and reheated evaporated milk has been of great value in many cases of infantile eczema. This is no doubt due to the reduced anaphylactogenic properties of heated milk, as so well shown by Ratner and Gruehl.[4] However, about 50 per cent of the patients with milk-sensitive eczemas, in our experience, did not tolerate the heated milk sufficiently well for us to be satisfied that it is the ideal milk substitute in this condition.

Hill and Stuart[5] and Tso[6] have shown that soybean can replace milk in the diet and that it fulfills the nutritional requirements of the growing infant. Prior to this series of cases we used sobee[5, 7] as a substitute for milk for a short time. Sobee, however, was not entirely satisfactory. It frequently caused diarrhea, excoriated buttocks, and vomiting in younger infants. Many older infants have persistently refused to take it, even to the point of starvation. It is not soluble in water and tends to settle out in the nursing bottle, requiring frequent shaking to facilitate its passage through the nipple. For the past several years, we have used a soybean emulsion* to replace milk in cases of infantile eczema as part of the regime to be described. The disadvantages mentioned above were not noted with this preparation.

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From the Allergy Clinic of the Children's Hospital of Michigan, Detroit.

*Kreme O'Soy, manufactured by Madison Foods, Madison College, Tenn., has the following composition as furnished by the manufacturer: protein (from soybean), 2.28 per cent; fat (soybean oil), 5.22 per cent; carbohydrate (from soybean and added dextrose), 4.45 per cent.

DIET

The diet consists of the soybean emulsion used to replace milk in the infant's formula. This is diluted with water in the same proportion as cow's milk would be diluted. Additional carbohydrate in the form of cane sugar is added, using from 2 to 4 tablespoons for the twenty-four-hour formula. We have yet to see a patient in whom cane sugar aggravated the eczema. It is apparently not antigenic. As has been shown,[8] the carbohydrates generally used in infant feeding are not antigenic. However, in a few cases we have felt that corn syrup and dextrimaltose have been the cause of some difficulty, and for this reason, we have used cane sugar exclusively. In infants over 5 months of age, sobee, used as a cooked cereal, is added to the diet. This should be cooked for about one hour until quite thick and firm. Some of the formula is poured over it. Two or three feedings a day are offered, in addition to the soybean "milk" formula. Sobee is not strictly a 100 per cent soybean food, since it contains some arrowroot flour and olive oil.

The possibility of sensitization to these items must be kept in mind as a cause of failure on this regime. For practical purposes, however, the diet as described, utilizing kreme o'soy and sobee, is essentially a total soybean diet. No other food is allowed for one week. There is probably a deficiency of vitamins on this diet, and it is felt that from one to two weeks is the maximum period for it to be maintained, without the addition of other foods or vitamins. The possibility of sensitization to soybean itself must be kept in mind. In this series of cases, there were two infants clinically sensitive to soybean, one of whom reacted very strongly to the skin test by the scratch method. The other did not react either by scratch or intradermal tests. It is not necessary to wait until the eczema is entirely cleared for the addition of other foods. We have found that, should this diet be effective, an appreciable improvement will be noted within a week. At that time those foods which are negative by skin test can be added to the diet, one at a time, every three to four days, and their clinical effect noted.

ENVIRONMENTAL CONTROL

The following instructions are given to the mother of each patient. The infant's bedroom should be as free from dust as possible. Efficiency in following out this order depends to a great extent upon the economic condition of the patient. This may account for the better results seen in private patients in contradistinction to those in the clinic patients. When possible, the mattress is enclosed in a nonallergic cover; failing this, it is wrapped in three or four heavy cotton sheets which are changed weekly. All feathers, carpets, drapes, and curtains are removed from the bedroom. All furry toys and animals are also removed. The floor

is oiled weekly. The mother and any other attendant is instructed to wear simple white cotton house dresses, to avoid silk clothing and silk stockings while in the infant's room, and to use nonallergic cosmetics. The infant is not to be removed from this room.

THE SEBORRHEIC FACTOR

Most cases have some seborrheic element. In several cases, we have seen all the symptoms dependent upon the seborrhea. The scalp with any tendency to seborrhea must be thoroughly treated. In the presence of seborrhea, it is almost impossible to clear up an eczema, despite the most careful attention to diet and environmental control. We have found that the most satisfactory method of treating the scalp is a thorough application, twice a day, of an ointment containing 1 per cent each of salicylic and benzoic acids. The skin beyond the hairline should be avoided. The scalp should be thoroughly washed with soap and water once a day, using a superfatted soap.

MECHANICAL FACTORS

All woolen clothing must be avoided. Woolen blankets should be enclosed between two heavy sheets sewn together to make a blanket cover. In this series of cases, only three positive skin tests to wool were found, two by the intradermal method and one by the scratch method. No positive patch tests to wool or crude lanolin were obtained. Yet clinically, in almost all cases of infantile eczema, wool is a definite irritant, probably on a mechanical basis, and for this reason it must be excluded.

SOAP AND WATER

Almost all writers on the subject of infantile eczema have overemphasized the harmful effect of bathing the infants. Many of the patients in this series had not been bathed for several weeks or even months, prior to seeing us. In our experience, most infants with eczema have done better with a bath several times a week. A daily bath was well tolerated in some cases. It is quite likely that the accumulation of skin debris, ointments, lotions, and perspiration results in a severe mechanical irritation of the skin. We have advised the use of several tablespoons of baking soda in the infant's bath. In only a few cases has bathing the infant caused an aggravation of symptoms, necessitating discontinuance of the bath. Most of the mothers have reported that the infants have been very much more comfortable after being bathed. The use of soap is contraindicated, except for washing the scalp in cases of seborrhea.

LOCAL TREATMENT

Local treatment is necessary for the control of symptoms and has been very well outlined in the papers of Hill,[1, 2] Rappaport and Hecht,[3] and Sulzberger.[9] In the main, our local treatment has followed the same

general lines and need not be repeated here in detail. We have used 5 per cent crude coal tar in zinc ointment most frequently for the dry, scaly eczema, and calamine lotion with or without phenol for weeping eczema. Other adjuncts to treatment, such as x-ray and ultraviolet therapy, have been used only rarely.

SKIN TESTING

While the above regime is being instituted, the following tests are made by the scratch method.

Whole milk	Bran
Casein	Wheat globulin
Lactalbumin	Wheat gliadin
Egg white	Wheat proteose
House dust	Oat
Kapok dust	Halibut
Wool	Feathers
Silk	Tomato
Orange	Cotton linters dust
Cod-liver oil	Soybean

If the scratch tests are negative, the tests are repeated intradermally, and all subsequent testing is done by the intradermal method. The egg white test is a good indicator of the ability of the skin to react to scratch tests. In general, the presence of a negative scratch test to egg white is a good indication that scratch testing will not be very productive. In this series of cases, two constitutional reactions to skin testing occurred, both to egg white by the scratch method. There have been no constitutional reactions to any of the intradermal tests provided they were done after negative scratch tests for the above list had been obtained.

DIET ADDITIONS

It should be emphasized that healing of the skin may be quite slow, but improvement, should it occur, will be definite on the above regime in a week or two. Without waiting for complete restitution of the skin to normal, one can make additions to the diet quite rapidly, excluding any foods which reacted by skin testing. In eighteen cases no skin tests were done. In some of these cases, the eczema was so widespread that no normal skin was available for testing. Passive transfer tests were not made in these cases. In the others, the patients were very young infants whose response to the basic diet and environmental control was very rapid, eliminating the necessity for testing. After institution of the regime as outlined above, dietary and environmental additions were made at from three- to five-day intervals. In this way, those factors clinically implicated were detected.

VITAMINS

In this series of cases, we have found several patients clinically sensitive to the common sources of vitamin C, such as orange, lemon, grapefruit, and tomato. For these infants we have used cevitamic acid, 50 mg. per day. In two patients, there was definite clinical sensitivity to cevitamic acid. Thiamin chloride should be added to the diet early

Fig. 1.—Patient aged 14 months. Generalized eczema since age of 5 months. No normal skin available for testing.

in the regime, since there is probably a marked deficiency of vitamin B_1 on the basic diet as outlined above. In cases of sensitivity to fish oils, we have used drisdol or some of the other synthetic vitamin D preparations. Carotene in oil has been a useful method of supplying sufficient vitamin A in cases sensitive to fish oil.

RESULTS

In seventy-one of the eighty-six patients (82 per cent) in this series, rapid improvement occurred on the above regime. In the majority of those benefited, complete restitution to normal occurred in from four to eight weeks. Multiple sensitivity was present in the majority of cases, both by skin tests and clinical observation. In the entire series, sixty-seven patients (77 per cent) were clinically sensitive to milk, either alone or in combination with other sensitivities.

Fig. 2.—Photograph showing almost complete restitution to normal six weeks after the patient in Fig. 1 was placed on a total soybean diet and under environmental control. During this period, the child was found clinically sensitive to milk and also unable to tolerate evaporated milk. She was clinically sensitive to all cereals except barley, to fish oil, orange juice, and many vegetables. During this period, she could take, without symptoms, kreme o'soy, sobee, beet, banana, barley, potato, prune, applesauce, cevitamic acid, drisdol, and thiamin chloride. All skin tests done subsequent to clearing of the eczema were still negative.

Fifty-one of the milk-sensitive patients were skin tested, and of these, thirty-five (65 per cent) reacted to one or more of the fractions of milk or to whole milk. Over one-half of the positive reactions to milk or its fractions were obtained by the intradermal method. Occasional delayed reactions to milk or its fractions occurred without preceding immediate

reactions. The specificity of delayed reactions to milk by the intradermal test was proved clinically in several of these patients. The improvement in the benefited patients who were not milk-sensitive was due to sensitivity to other items which were excluded on the basic diet and in the controlled environment. By addition to the environment and diet, in combination with the skin testing, these sensitivities were detected. Restoration of tolerance to the offending foods occurred quite rapidly in some cases. One milk-sensitive patient whose eczema cleared up very rapidly was able to take a powdered milk preparation, previously not tolerated, six weeks after it was eliminated from the diet, without relapse. Most milk-sensitive infants, previously unable to tolerate evaporated milk, were able to take it in from six to twelve weeks. However, a few patients who were milk-sensitive, under observation from time to time for several years, have continued to be highly sensitive to milk in any form, including evaporated milk. The restoration of tolerance to milk while on a milk-free diet as seen in most of the patients is at variance with the recommendations of Ratner,[10] who feels that it requires the gradual addition of raw milk to the diet in order to overcome an existing sensitivity to cow's milk. We have observed, however, that acquisition of tolerance to other foods also occurred quite rapidly in many infants, provided the offending foods were eliminated from the diet for from two to four months.

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469 FISHER BUILDING

THE PREVENTION OF MEASLES IN A BOYS' CAMP THROUGH THE USE OF IMMUNE GLOBULIN (MEASLES ANTIBODY)

ERIC DENHOFF, M.D.
BOSTON, MASS.

THE effective control of measles in a situation where the spread of the disease would have seriously interfered with the activities of a group is illustrated in the following report of an incident in July, 1939, at Camp Arnold for Boys, Cornish, Me. The observations in this threatened outbreak of measles confirmed the effectiveness of the use of immune globulin (human) for the prevention of the disease where intimate exposure may be presumed to have occurred.

Satisfactory methods for the prophylaxis of measles have been slow in development, despite the public health significance of this disease. At present no adequate control can be exercised except that which is available through the use of human immune bodies in the form of adult immune serum or whole blood, convalescent serum, and more recently, immune globulin (placental extract). Both convalescent serum and adult immune serum had been found to be effective in the prevention of the disease, but their large scale use was prohibited by the lack of adequate supply. The human placenta and the blood contained in it have been found to furnish a source of antibodies against measles comparable in potency to the antibody content of adult immune serum. By concentration of this material, a globulin fraction was obtained which was equal to, or sometimes more potent than, fresh convalescent serum. Reports of the use of immune globulin so prepared show that it has been effective in producing prevention or modification of measles in approximately 95 per cent of the cases. Reactions to the injection of immune globulin have, however, been troublesome in some instances.

The Outbreak in Camp.—On July 7, 1939, six days after the camp opened, a 6½-year-old boy developed definite signs of measles. He was observed in the dining hall with a discrete papular rash on both cheeks. On further examination a diagnosis of measles was made, and the boy was discharged home, where he passed through a typical course of the disease. The camp at this time had seventy-eight enrollees, ranging in age from 4 to 16 years. There was, in addition, a staff of twenty-four adults. Of this total group of 102 camp residents, sixteen children, two councillors, and the camp nurse had not had measles previously. Seven of the sixteen boy campers had been in intimate contact with the patient. He was known to have coughed in the nurse's face during examination. He had been swimming with one councillor the previous day, had lived

in a cabin with several other nonimmune children, and had had contact in the dining hall and elsewhere with the remainder of the nonimmune group.

A first injection of immune globulin, 2 c.c. for each person, was given intramuscularly into the buttocks to sixteen boys and to the nurse twenty-six hours after the diagnosis had been made on the patient. No variation was made for age, weight, height, or for intimacy of contact among the individuals. It was felt that a standard dose might be satisfactory because it seems established that exposure is less intimate and measles less often follows in institutions and in large groups than in the home. Furthermore, it was impossible to determine the extent of exposure among the patients so treated. All of the patients were first skin tested with the immune globulin. There were no positive reactions, although two patients were known to have allergic backgrounds and were under treatment for various allergies at the time. The instruction sheet accompanying the immune globulin did not mention the necessity of performing skin tests. However, reactions to these proteins of human origin have been reported in a few instances. Four days later, the 2 c.c. dose was repeated. This change in the recommended technique was made to insure, in so far as possible, protection in these patients and also to minimize the possibility of reaction. It was estimated that the first injection was given to the exposed person on the fourth day after the beginning of the period of possible exposure, and the second injection, on the eighth day. Because of an inadequate supply of serum, two adults who had not had measles previously were not injected, and thus became involuntary controls.

In addition to the injection of serum, some degree of isolation precautions was attempted. The camp routine was altered to diminish the possibility of contacts among the nonimmune children. Examinations were made twice daily for evidence of initial symptoms of measles, and campers and councillors alike were instructed to report the slightest evidence of illness. Eleven days following the development of measles by the exposee (Case A), one councillor, aged 21 years, who had not had measles previously, who had been swimming with Case A, and who had not been injected with immune globulin, developed headache, malaise, and coryza. Forty-eight hours later he developed typical measles (Case B). He was immediately removed from the camp. No further cases of measles developed, although two children, aged 6 and 7 years, who had received the injections of immune globulin after exposure to Case A slept in the same quarters with the councillor (Case B), until he developed the evidences of the disease.

Reactions.—The administration of immune globulin has been reported to be followed in some instances by immediate or delayed local reactions, and occasionally by general reactions. The local reactions consist of

redness, tenderness, and swelling at the site of injection, while general reactions have consisted of mild febrile responses. In one large series, 36 per cent of the persons injected had local reactions, and 5 per cent moderately severe; 19 per cent had a definite general febrile response, but in only 3 per cent did the temperature rise above 101° F. Twelve of our seventeen persons had some general reaction, one of which might be classed as severe. There were no local reactions.

The camp nurse, eight days after exposure to Case A and four days after the last injection of immune globulin, developed an acute bronchitis with a harsh cough, some râles in the chest, and a temperature of about 100° F. This illness persisted for ten days and necessitated bed care. No eruption of any sort appeared to indicate that this might have been a modified, attenuated measles.

The moderate reactions suffered by the six patients consisted of slight rhinitis, pharyngitis of three days' duration, and a slight cough, with an elevated temperature averaging 99°. The other six children developed only rhinitis, without any elevation of temperature. These reactions to the injection of the immune globulin, if such they were, developed from six to ten days after the first injection, reached a peak in twenty-four hours, and then gradually subsided. The younger children who, in relation to age and weight, received a larger dosage of the serum had milder reactions or were symptom-free. Although there were no rashes developing in these patients, the lack of similarity of the symptoms in the patients who received the serum to the characteristic reactions reported in the literature raises the question as to whether the symptoms were not those of markedly modified measles. All developed symptoms at approximately the same time—at a period several days after the injections—when colds were not present among the other campers. It would seem that a measles epidemic was controlled in its initial stages, without marked alteration of camp routine.

SUMMARY

A case of measles developing in a boys' camp with 102 campers exposed nineteen nonimmune children and adult members of the personnel. Seventeen of the group received immune globulin in two doses of 2 c.c. each, separated by an interval of four days. Reactions of the type described in the literature were not observed. One councillor who was not given serum developed the disease. Twelve of the sixteen children who received the serum developed almost simultaneously mild symptoms of upper respiratory infection three or four days after the second injection. No definite signs of measles appeared in any of this group. Nevertheless, it was felt that this may have been measles, markedly modified by the use of serum. The prophylactic injection of immune

globulin for the prevention of measles seemed to arrest promptly a threatened outbreak of measles in the boys' camp.

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PNEUMOCOCCUS PERITONITIS IN NEPHROTIC AND NON-NEPHROTIC CHILDREN

A Comparative Clinical and Pathologic Study With a Brief Review of the Literature

Marcel Pahmer, M.D.
New York, N. Y.

AN ANALYSIS is presented of twenty-nine cases of pneumococcus peritonitis observed in the Babies Hospital of the City of New York during the last nineteen years. The findings cast some light upon the pathogenesis, diagnosis, and treatment of the disease. The material is divided into two series: twelve cases in patients who were otherwise well, and seventeen cases in patients with nephrosis. Only patients in whom the diagnosis of peritonitis was made during life are included in the study. This criterion excludes four cases of pneumococcus peritonitis revealed by post-mortem examinations.

INCIDENCE

Except in children with nephrosis, pneumococcus peritonitis is not a frequent disease. The following citations throw light upon its frequency. It forms about 2 per cent of all acute abdominal emergencies in childhood.[1] Barrington-Ward[2] saw twenty cases in fifteen years; Bass[3] observed nineteen cases in twelve years; Guilleminet[4] reported thirty-four cases seen between 1919 and 1929; and Ladd and associates[5] recorded twenty patients between 1929 and 1939. Finally, among 125 cases of diffuse peritonitis observed in five years by Heiman,[6] only fifteen were due to pneumococcus; Cole[7] contrasted twenty-six instances of pneumococcus peritonitis observed in eighteen years with 445 cases of acute appendicitis operated upon in the same period.

Despite the statement by Johnston[1] that localized peritoneal abscess is twice as frequent as diffuse peritonitis caused by pneumococcus, the incidence of peritoneal abscess is small compared with the diffuse type. The proportion of abscesses in the series of Cole[7] and of Heiman,[6] numbering sixteen and fifteen cases, respectively, was about 25 per cent. These findings are similar to ours. In our twelve non-nephrotic children, generalized infection of the peritoneum was present in nine cases, and peritoneal abscess in three, or 25 per cent.

The literature contributes little regarding the incidence of peritonitis in nephrotic subjects. Tappan[8] reported thirteen cases of peritonitis (28 per cent) in a group of forty-five children with nephrosis,

From the Pediatric Section of the Vanderbilt Clinic.

and Lyttle[9] recorded five deaths due to peritoneal infection in seventeen nephrotic children.

In our series, pneumococcus peritonitis occurred in seventeen children with nephrosis, or in 33 per cent of the total number of nephrotic patients observed in this institution during a period of eight years (1931-1939). Only one case of peritoneal abscess with fistula was observed in this group, all others being of the diffuse type.

AGE

Pneumococcus peritonitis is a disease of childhood, the period of maximum incidence varying between 2 and 13 years of age.[4, 7, 10, 11] In our group, generalized peritonitis developed in three non-nephrotic children of 3 and 4 years of age; in two cases of 5 and 6 years; in three of 7 and 8 years; and in one of 10 years. Peritoneal abscess was present in three patients, aged, respectively, 18 months, 3 years, and 7 years. In nephrotic children, twelve cases, or 70 per cent, occurred between the ages of 2 and 5; two occurred in the second year, one in the seventh, one in the eighth, and one in the twelfth year of life. One peritoneal abscess was observed in a boy aged 3 years.

SEX

The question of the sex of patients with peritonitis is of importance in relation to the pathogenesis of the disease. Observers are unanimous in indicating its large preponderance in the female sex.[1, 6, 7] Mathieu[12] and Leopold[13] each recorded 100 per cent girls; Lipschutz[10] recorded twelve girls and one boy. McCartney and Fraser,[11] in a careful study of fifty-six cases, found primary peritonitis in forty-four girls; no girls in their series had a secondary type of infection. They interpret these findings as indicative of the importance of the genital route of infection in pneumococcus peritonitis. In our series, all twelve non-nephrotic patients were girls. In the children with nephrosis, only five were girls, with twelve cases of peritonitis occurring in boys.

MORTALITY

So many factors affect the prognosis for pneumococcus peritonitis in children that it is difficult to assess the published statistics concerning its death rate. Lipschutz[10] records 100 per cent mortality; Leopold,[13] 71 per cent; Bass,[3] 58 per cent; McCartney and Fraser,[11] 42 per cent; Rohr,[14] only 13.7 per cent. The majority agree that the outlook is serious.

The following factors, among others, influenced the final outcome of the disease in our series.

1. *Age.*—This plays a minor role in non-nephrotic children, as shown by Fig. 1. In nephrotic subjects, nine patients, or 75 per cent, died

between 1 and 5 years of age, while only three, or 50 per cent, died between the ages of 6 and 12.

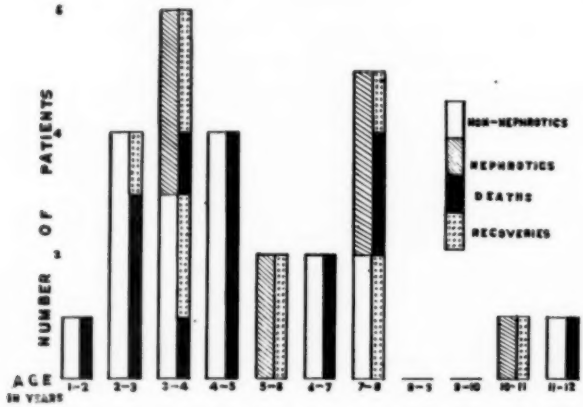

Fig. 1.—Age distribution of pneumococcus peritonitis in nephrotic and non-nephrotic children and the relation to the mortality rate of the disease.

2. *Type of Peritonitis.*—All cases in the non-nephrotic group had primary peritonitis. The mortality was 33 per cent in the diffuse form and 66 per cent in the three cases of peritoneal abscess. This last result is not in agreement with the opinion often expressed, that patients who survive the acute stage of the disease usually recover even if an abscess develops.[1] In the nephrotic group, all three patients died whose peritonitis was secondary to a previous focus (pulmonary in these instances). Of thirteen children with primary generalized peritonitis, ten, or 77 per cent, died. Finally, the one patient with peritoneal abscess died.

3. *Sex.*—Our twelve non-nephrotic patients were girls; five, or 41 per cent, died. In the nephrotic group, five patients were girls, with a mortality of 80 per cent. Twelve patients were boys, with a mortality of 75 per cent. These findings represent a total mortality of 76 per cent in this entire group. The findings are similar to those of McLeod and Farr[15] who reported 70 per cent in ten cases and of Tappan[8] with 61.5 per cent in thirteen cases; they are higher, however, than Lyttle's[9] findings of 53 per cent mortality in seventeen cases.

4. *Duration of Nephrosis.*—The time of appearance of pneumococcus peritonitis in nephrotic children has not attracted much attention. It is interesting to note two trends in our series. In one period, extending from one to eight months after the onset of the nephrotic syndrome, there were nine deaths, or 75 per cent, in twelve cases; in the second period, extending from twelve to twenty-two months after the onset of nephrosis, three patients out of six, or 50 per cent, died. This suggests a tendency for patients who have had nephrosis for a longer time

to offer relatively more resistance to this form of pneumococcal infection than those whose nephrosis is of recent appearance (Fig. 2).

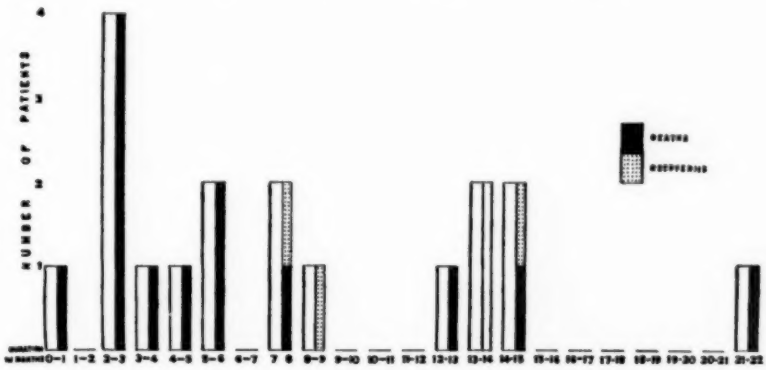

Fig. 2.—Incidence of pneumococcus peritonitis in children with nephrosis. The death rate of the infection is highest in the early stage of nephrosis.

5. *Bacteriologic factors* and *therapeutic measures* will be considered in a later section.

In summary, whatever the respective role of these factors may be, a fatal outcome in pneumococcus peritonitis is to be expected in a large proportion of cases.

CLINICAL FEATURES

The clinical picture as exemplified in each group offered some noteworthy distinctions.

The *onset* was usually sudden and severe in non-nephrotic children, while in patients with nephrosis it was sometimes more insidious.

Abdominal pain and *vomiting* were present in all cases of the first group. Usually periumbilical, the abdominal pain was sometimes referred to the epigastrium, either iliac fossa, the flank, or the suprapubic region. In nephrotic patients these symptoms were often capricious in their appearance and transient in duration. In fourteen cases, they occurred while the child was under observation in hospital.

Diarrhea is a symptom of capital interest. It is said to appear early in the course of the disease and to be often profuse and accompanied by tenesmus. Not infrequently the stools are stained with mucus or blood. Some authors[12, 16, 17] regard diarrhea as of etiological significance. Others have not observed it in the early stages, or they have even seen persistent constipation throughout the disease. Cole[7] found diarrhea in only 30 per cent of his cases; Wile and Saphir,[18] in ten of twenty-four cases. In our series, none of nine non-nephrotic children with generalized peritonitis presented diarrhea. In one case of peritoneal abscess, it was of marked severity. In nephrotic patients, seven of seventeen children, or 41 per cent, had definite diarrhea.

The *constitutional manifestations* were those of a severe infection.

Physical examination revealed the most conclusive signs of the disease.

Abdominal tenderness was a constant feature in non-nephrotic children. It was marked in seven patients, and moderate in only two cases. Although distributed generally throughout the entire abdomen, it was often maximal at some particular site; it appeared six times in the right lower quadrant, and once in the lower abdomen. On the contrary, in the nephrotic group only four of seventeen patients showed a localization of maximal tenderness, which appeared twice in the right lower quadrant and twice in the left lower abdomen.

The presence of *abdominal distention* depended upon the previous condition of the abdomen. In children with nephrosis, it became extreme in two cases, was conspicuous in two others, and in the remaining thirteen cases, was either moderate or absent. In the other group, only twice was its presence significant at an early stage.

Muscular rigidity appeared early in non-nephrotic patients and was usually widespread, but, as a rule, less conspicuous than in perforative peritonitis or severe appendicitis. The differentiation from the latter condition was exceedingly difficult when the maximal resistance was localized in the right lower quadrant, as was the case in seven of our patients. In the nephrotic group, muscle defense reached a boardlike quality in only one patient. Owing to the stretching of the abdominal wall by ascites, the other cases exhibited little or no defense.

Once the diagnosis of acute peritonitis suggests itself, the following features may be considered as offering possible support for a pneumococcal etiology.

Facial herpes, although often referred to in the literature,[17, 19, 20] was noted in only three instances in non-nephrotic patients, twice on admission and once five days postoperatively. None of our patients with nephrosis had herpes.

The presence of *upper respiratory prodromes* is frequently characterized as an important lead in the diagnosis of an obscure abdominal lesion.[1] It was found in 90 per cent of Lipschutz's cases.[10] Other observers[13, 18, 20] have not encountered it so frequently. In our non-nephrotic group, four, or 25 per cent, of the patients gave a recent history or evidence on admission of an upper respiratory infection such as tonsillitis, nasopharyngitis, or sinusitis. The proportion was increased to 70 per cent in the nephrotic group. This difference between the two groups is not surprising in view of the fact that the pneumococcus is harbored in the upper respiratory passages of nephrotic patients sometimes many weeks before the onset of the peritoneal manifestations (Hartman, quoted by McLeod and Farr[15]). Furthermore, many observers regard these passages to be the portal of entry of the causative organism, which is then carried to the peritoneum by way of the blood stream.

Vulvovaginitis.—Considerable work has accumulated in relation to the possibility of an ascending infection through the genital tract in girls with pneumococcus peritonitis. Clinically, few instances of vulvovaginitis are recorded: one in 13 patients of Cole[7] had vaginal discharge; one in ten patients of Loutsch;[20] and three in thirteen patients of Lipschutz.[10] In our group of twelve non-nephrotic children, only one showed definite evidence of vulvovaginal infection, and none of five girls with nephrosis showed evidence. Nevertheless, it is not necessary that a lesion of the genital tract be demonstrable in order to prove the passage of the organism.[13] The bacteriologic findings are more frequently positive than the clinical. Furthermore, participation of the pelvic organs in the peritoneal inflammation is sometimes revealed by dysuria or suprapubic pain, as was the case in two of our non-nephrotic patients. Thus, inspection of the vulva and culture of the vaginal secretions are indicated in all girls with pneumococcus peritonitis.

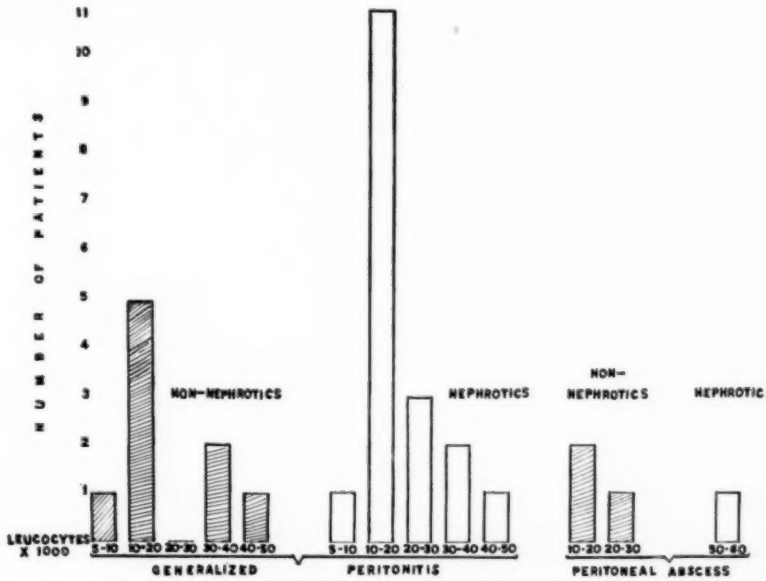

Fig. 3.—White blood cell counts in nephrotic and non-nephrotic children with generalized peritonitis and peritoneal abscess.

DIAGNOSTIC LABORATORY PROCEDURES

White blood counts in pneumococcus peritonitis, as a rule,[6, 10, 17, 21, 22] are said to reveal a higher leucocytosis than in severe acute appendicitis, although counts between 20,000 and 30,000 are sometimes encountered in the latter.[17] Fig. 3 shows the hematologic changes observed in both

groups of our series. In 64 per cent, the number of leucocytes did not exceed 20,000. The differential count was practically identical in the two groups, averaging about 81 per cent polymorphonuclear cells.

Bacteriologic Findings.—Pneumococcus Type I appears to be the commonest organism in non-nephrotic patients.[5, 6, 7, 13, 21] Leonardo (quoted by Glazier[22]) collected twenty-six cases prior to 1929. Sixteen were of Type I, three of Type II, and three of Group IV. In patients with nephrosis, Group IV seems more frequent.[8, 23] The separation of the components of Group IV has not disclosed preeminence of any single type from Type IV to Type XXII.

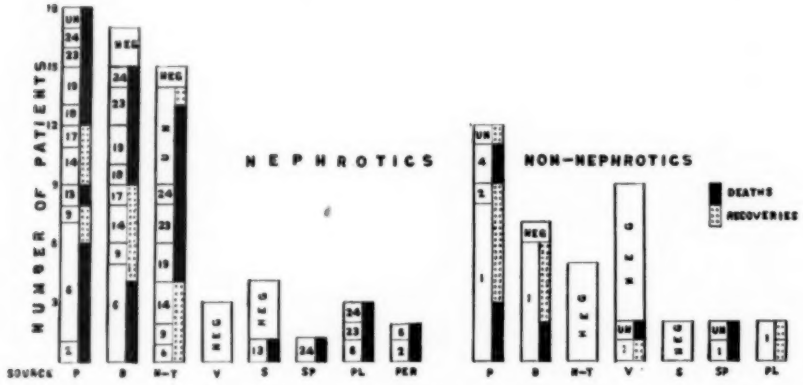

Fig. 4.—Bacteriologic findings and their relations to the mortality rate in nephrotic and non-nephrotic children with pneumococcus peritonitis. (The numerals within the blocks refer to the type of the organism. *NEG*, culture negative for pneumococci; *UN*, pneumococcus present but not typed; *P*, peritoneal fluid; *B*, blood; *N-T*, nose and throat exudates; *V*, vaginal secretions; *S*, sputum; *SP*, spinal fluid; *PL*, pleural fluid; *PER*, pericardial fluid.)

The bacteriologic findings in our series are demonstrated in Fig. 4. In the non-nephrotic group no use was made of abdominal puncture, which has proved a valuable method in the hands of various authors.[24, 25] In all our cases except one in which a peritoneal abscess ruptured spontaneously through the abdominal wall, the peritoneal fluid was obtained at operation. In 66 per cent, pneumococcus Type I was cultivated; 50 per cent of these patients recovered. In the nephrotic group, 35 per cent yielded Type VI; not one showed Type I. It is of interest to note that in one nephrotic boy aged 7 years, two attacks of peritonitis occurred, separated by an interval of seven months. A different organism was recovered in each instance, Type IX on the first occasion, Type XVII on the second. Despite repeated cultures, this second type had not been demonstrated during the first attack. In a 2-year-old girl, two attacks of peritonitis occurred two weeks apart. The same organism (Type XIV) was found in both instances. These two patients recovered.

The presence of *bacteriemia* in nephrotic patients was associated with a mortality of 66 per cent, or twice that of the non-nephrotic group.

Nose and throat cultures were taken in five patients of the non-nephrotic group; none yielded the organism, although two of these five patients showed definite clinical evidence of upper respiratory infection. In seventeen patients with nephrosis, only two nasopharyngeal cultures failed to show the pneumococcus.

We were not so successful as McCartney and Fraser,[11] who found ten positive *vaginal cultures* in ten patients, nor as Bass,[21] who reported seven positive results in nineteen cases. In our series, three vaginal cultures were negative for pneumococci in girls with nephrosis, and in seven of nine non-nephrotic children. One girl with a positive culture had definite vaginitis clinically; the other was a patient with peritoneal abscess.

Pneumococcus was found in only one of six *stool cultures*. This was in a nephrotic boy whose stools showed Type XIII two days before and two days after peritonitis had set in. The other five negative stool cultures were taken from girls, one of whom had a positive vaginal culture. These observations fail to support the frequently made assertion that the vagina is contaminated by the feces.

In summary, a bacteriologic diagnosis was established postoperatively in all cases of the non-nephrotic group. In children with nephrosis, the presence of the organism in the oral and abdominal cavities and in the blood facilitated the recognition of the disease at an early stage.

SURGICAL TREATMENT

Contemporary opinion favors conservative management of pneumococcus peritonitis in children if the diagnosis can be made without recourse to surgery. Nevertheless, it is impossible to get data on a series of cases treated by nonoperative methods, even though occasional reports on a single case are accessible. The success of surgical intervention appears to depend mostly upon the time when operation is performed. The consensus[7, 16, 17, 21, 26, 27] favors delay of operation until after the end of the bacteriemic stage. Delay is especially indicated when the evidence points to abscess formation. The mortality varies between 30 and 77 per cent in various series.

In our series, operation was performed only in non-nephrotic patients. Nine cases had generalized peritonitis and two had peritoneal abscess. The mortality was modified by the following factors:

1. *Type of Operation.*—Appendectomy with drainage of the peritoneal cavity was performed in five cases, with two deaths; appendectomy without drainage was done in two cases, with one death; incision and drainage were performed in two cases of generalized peritonitis, with no deaths, and in two cases of abscess, with one death.

2. *Time of Operation.*—Of five patients operated upon one or two days after the onset, only two died. Of four patients operated on between the third and sixth days of the disease, two died. Finally, one abscess was incised on the eleventh day, and the patient died; another was incised on the forty-second day, with recovery.

3. *Age of Patient.*—The outcome was apparently not modified by the age of the patient (Fig. 1).

4. *Complications.*—In four cases, or 25 per cent, of the non-nephrotic group, residual abscesses developed after the original operation and required intervention. None of these patients died. Disruption of the abdominal wound occurred in one case with recovery. Secondary infection of the abdominal incision occurred twice, once with the Klebs-Löffler bacillus in a patient who subsequently died of diphtheria. Empyema developed in two cases; thoracotomy proved successful in both. In a few instances metastatic infections of the subcutaneous tissue required additional surgery; the pneumococcus yielded by these infections by culture was always the same as that in the peritoneal fluid.

In summary, the general mortality for this group was 41 per cent, 33 per cent in the diffuse form, and 66 per cent in the cases with abscess. These rates compare favorably with previous reports. As will be seen, however, four patients of this group also received serum postoperatively, which probably altered the outcome.

SERUM TREATMENT AND CHEMOTHERAPY

Until 1938, when sulfapyridine became available, serum therapy represented the most important specific adjunct to therapy in pneumococcus infections. In the rare instances on record in which serum alone was used, the results have not shown the same beneficial effects as in other pneumococcal infections.[6, 7, 9, 10, 22] Even in the favorable instances reported,[5] serum treatment was used in conjunction with surgical intervention.

In our series, twelve patients were treated with antipneumococcus serum: eight were children with nephrosis, and four belonged to the non-nephrotic group. The results of this treatment are demonstrated in Table I.

Of the non-nephrotic cases, three patients with generalized peritonitis were treated with serum after operation. All three recovered; in six cases treated by operation alone, three died. Nevertheless, doubt arises concerning the respective value of serum and operation in the three cases treated by both measures. It can be seen that two patients (Cases 7 and 8) received fairly adequate dosage (180,000 and 280,000 International Units, respectively), while one patient (Case 9) recovered despite a very small amount (30,000 I.U.).

Only one of three patients with peritoneal abscess received serum, a 7-year-old boy suffering from peritoneal abscess with fistula. Serum treatment was instituted three days after admission, but only 60 c.c., or approximately 70,000 I.U., were given. The patient died a few days later.

Eight patients with nephrosis were treated with serum of various types, with 75 per cent mortality. Recovery resulted in two children whose infection was limited to the peritoneal cavity and who received serum in appropriate dosage. Four of the patients who died received inadequate amounts. Patient 29 died suddenly during the injection of serum; only 20 c.c. of serum were administered to patient 5; patients 19 and 25 received serum in the terminal phase of the illness. Two patients, however, died despite adequate amounts of serum. Patient 22 died suddenly one-half hour after the injection; patient 24 did not improve clinically and died after discontinuance of the serum.

In the discussion of the effects of serum treatment, three points deserve closer attention:

Reactions to Serum.—Although only one patient suffered from serum sickness, in many instances serum treatment brought about untoward reactions, such as spiking fever, chills, thready pulse, cyanosis, etc., despite careful testing before the beginning of the treatment. These reactions occurred mostly in children with nephrosis, among whom the two instances of sudden death were also encountered.

Effects on Bacteriemia.—The twelve patients treated with serum all had bacteriemia before serum injections were started. The treatment did not, however, invariably sterilize the blood stream. In one of the patients without nephrosis a negative blood culture was obtained temporarily following serum treatment, but the sterilizing effect of the serum did not persist a long time. In another patient, blood cultures were still positive during and after treatment. In two children, no blood cultures were obtained after serum treatment.

In patients with nephrosis, negative blood cultures were obtained in five instances after serotherapy. This represents 62.5 per cent of the total number exhibiting bacteriemia, or twice the number in the non-nephrotic group. In three patients who died suddenly during or shortly after serum injection, no blood cultures had been taken during life. Blood obtained post mortem, however, still yielded the organism. Finally, one patient received serum on the last day of life and a blood culture taken that same day was still positive for pneumococci.

Complications.—Despite serum treatment, complications frequently set in. Pneumonia occurred in 25 per cent of both groups, not including two cases of bronchopneumonia; meningitis occurred in two patients, both of whom died. A peculiar erysipeloid lesion of the inguino-abdominal region, resistant to serum injections, was observed in nearly

TABLE I

SERUM THERAPY

CASE	AGE (YR.)	SEX	DURATION SINCE ONSET	ORGANISM FIRST RECOVERED FROM ABDOMEN		BACTERIEMIA		TYPE OF PERITONITIS	OPERATION		SERUM			COMPLICATIONS	OUTCOME
				TYPE	DAY	BEFORE SERUM	AFTER SERUM		TYPE	DAY OF DISEASE	TYPE	DAY OF DISEASE	TOTAL UNITS		
Non-Nephrotic Children															
7	5½	F	1 day	I	1st	+	0	Generalized primary	Appendectomy Drainage	1st	I	5–35	190,000	Empyema; residual abscess	Recovered
8	3½	F	1 day	I	1st	+	†	Generalized primary	Appendectomy Drainage	1st	I	3–12	285,000	Lobar pneumonia; bronchopneumonia; residual abscess	Recovered
9	5½	F	6 hr.	I	1st	+	+	Generalized primary	Appendectomy Drainage	1st	Polyvalent	3–5	30,000	Empyema; parietal abscess	Recovered
11	7	F	3 wk.	I	3 wk.	+	†	Peritoneal abscess	–	–	I	25–26	72,000	Pneumonia; meningitis	Died
Nephrotic Children															
14	2	F	In hospital	XIV	2nd	+	0	Generalized primary	–	–	XIV	2–16	200,000	Conjunctivitis	Recovered

14	2	F	In hospital	XIV	2nd	+	0	Generalized primary	–	–	XIV	2–5	140,000	Serum sickness	Recovered
15	11	F	In hospital	XVIII	1st	+	+ (Post mortem)	Generalized primary	–	–	XVIII	1	24,000	Pleurisy; meningitis	Died
19	6	M	In hospital	VI	3 days before death	+	+	Generalized primary	–	–	I and II	1	42,000	–	Died
22	2	M	1 day	XIX	Post mortem	+	+ (Post mortem)	Generalized primary	–	–	Rabbit XIX	2	300,000	Died suddenly ½ hr. after treatment	Died
24	14 mo.	M	1 day	VI	Post mortem	+	0	Generalized primary	–	–	VI	2–4	216,000	–	Died
25	4½	M	In hospital	XIX	1st	+	0	Generalized primary	–	–	XIX	?	60,000	Bronchopneumonia	Died
27	3½	M	1 day	VI	1st	+	0	Generalized primary	–	–	VI	2–5	242,000	Multiple cutaneous abscesses	Recovered
29	6½	M	In hospital	XXIV	22nd	+	+ (Post mortem)	Generalized primary	–	–	XXIV	42–43	12,000	Meningitis. Died suddenly during serum administration	Died

one-third of the nephrotic patients. This is supposedly due to superficial inflammation of the soft tissues covering a peritoneal diverticulum (Fèvre[17]). Even in the cases in which the organism disappears from the blood stream, it can still be found in the upper respiratory passages many weeks after serum has been discontinued, and, hence, may become the source of a new peritoneal inflammation.

If the use of serum in the treatment of pneumococcus peritonitis has been disappointing, the recent results with chemotherapeutic measures have been more gratifying. Unfortunately, the use of sulfanilamide and its derivatives had not been developed at the time when most of our cases were observed. Only two children with nephrosis were treated by this method.* One was a boy, aged 6½ years, who was treated in the hospital for nephrosis of a few months' duration. Peritonitis developed twenty-two days after admission. The abdominal fluid and blood both yielded pneumococcus Type XXIV. Various methods of treatment, including intravenous injection of sulfapyridine, proved of no avail, and meningeal symptoms appeared. The patient died suddenly during an injection of serum (Table I, Case 29). Another nephrotic boy, aged 7 years, developed pneumococcus peritonitis while under observation in the hospital. Abdominal, blood, and throat cultures showed pneumococcus Type IX. The patient received sulfapyridine orally and intravenously for fifteen days. The blood culture became sterile the second day, but nose and throat cultures still showed the organism four weeks later. Nevertheless, the patient recovered from this first attack. Two weeks later a new peritoneal syndrome appeared, this time with Type XVII in both the blood and peritoneal exudate. The same treatment was instituted for seven days. The organism disappeared from the blood twenty-four hours after the beginning of the treatment, and the patient recovered.

PATHOGENESIS

Three principal routes of infection are alleged to be of importance in the pathogenesis of pneumococcus peritonitis: the blood stream, the genital tract, and the gastrointestinal tract. The lymphatic system is usually thought to be a secondary pathway.

Blood-borne Infection.—It is suggested that the organism reaches the peritoneum through the blood stream from an initial focus. The latter is commonly found in the upper respiratory passages.[7, 10] Many objections are raised against such an interpretation. Although bacteriemia is frequent in pneumonia, it rarely results in peritonitis. Elkin[28] found only three cases of peritonitis in 1,908 cases of pneumonia; Rischbieth,[29] one case in 6,000; Rolleston,[30] eleven in 4,454. Experimentally, the intravenous injection of pneumococci causes neither pneumonia nor peri-

*Four patients with nephrosis, not included in this series, have since been treated successfully by sulfapyridine, with striking results on the clinical picture and the bacteriemia.

tonitis, but septicemia,[31] and intraperitoneal injection of the organism is followed in a few minutes by the appearance of the pneumococcus in the blood stream. Even if it is carried by the blood stream, it is surprising that it should infect the peritoneum, usually a resistant membrane, rather than other sites of predilection such as meninges, pleurae, lungs, etc.[32] To explain adequately the infection of the peritoneum requires the additional hypothesis of an intermediary lesion such as abscess of the peritoneal wall or of the intestine, or infection of a thrombus. Actually lesions such as these are exceptional.[18] These considerations suggest that septicemia is secondary to an extraperitoneal infection.

Vaginal Infection.—The predominance of the disease in the female sex and the frequent occurrence of vaginitis, clinically and bacteriologically, in patients with pneumococcus peritonitis have led some authors to propose a genital route of infection. Peritonitis, however, occurs also in boys. Pathologic data related to the genital participation of the generalized peritonitis are not conclusive. McCartney and Fraser[11] stress the analogy between gonococcus salpingitis and pneumococcus infection of the genital tract. They found that the pouch of Douglas always contains more pus than the rest of the peritoneal cavity. They observed at operation that the infection in its early stage was usually limited to the pelvis; the fimbriae and the tubes showed congestive changes, and on several occasions pus could be expelled from the lumina of the tubes. Experimentally, an ascending current in the vagina has been demonstrated by the dye method. However, even if the pneumococcus is added to the colored fluid, lesions of the tubes and uterus are exceptional (Bound, quoted by Glazier[22]). The latter findings suggest that the catarrhal state of the tubes as observed in pneumococcus peritonitis is due to their participation in the generalized inflammation and that the presence of the organism in the tubes is a secondary, not a primary, phenomenon.

Gastrointestinal Route.—The frequency of diarrhea and the occasional finding of pneumococci in the stools of patients with peritonitis seem to point to the possibility of a primary gastrointestinal lesion. The pneumococcus is presumed to reach the intestine by way of the oral cavity.[13, 19] This would explain the constant finding of generalized abdominal tenderness, especially marked in the right lower quadrant, and the frequently gangrenous aspect of the head of the cecum at operation.[13] Others[18] have found various lesions of the gastrointestinal tract by careful histologic examination, or they believe in the passage of the organism through an intact mucosal layer of the intestine.[18] However, attempts to produce pneumococcus peritonitis experimentally by feeding large doses of the causative organism to rabbits have failed consistently.[11, 33, 34] Despite the great number of upper respiratory and pulmonary infections in which pneumococcus is present, the occurrence of peritonitis remains comparatively rare. As in the case of tubal lesions, the organism in

clinical cases of pneumococcus peritonitis resides not in the lumen of the intestine but in the serosa. The same observation is true of the appendix and explains the misinterpreted cases of pneumococcus appendicitis reported in the literature.

Lymphatic Route.—This is rarely invoked since the clinical picture of peritonitis is that of fulminating sepsis. The rare cases of lymphaticostomy that have been carried out therapeutically have ended in failure.

This brief review of the pathogenesis of the disease forces one to the conclusion that the peritoneum may be infected through more than one channel and that no theory embraces and explains all cases. Our own pathologic findings corroborate this point of view.

PATHOLOGY

The consistency with which we found bacteriemia, associated frequently with infection of the upper respiratory passages, has been previously analyzed.

The pelvis and the pelvic organs were explored in seven cases of the non-nephrotic group. In none was any abnormality reported. In only one patient with nephrosis were there congestive changes in the pelvic organs, and four other autopsy examinations in this group yielded entirely negative findings. In no case of either group was the organism found in the lumen of the tubes or uterus.

Gastrointestinal examinations yielded different results in each group. In the non-nephrotic cases, the appendix was removed at operation in nine patients with generalized peritonitis. Six microscopic examinations demonstrated that the changes were most marked in the outer coats or the serosa, the mucosa showing little or no alteration. Three cases showed no appendiceal lesions at all. In no instance was the pneumococcus found in the lumen of the appendix. In patients with nephrosis, seven autopsy examinations were performed. Except in one case in which a small ulceration of the esophagus was found and another in which the gastric mucosa showed superficial erosions, both organs were normal in all other instances. The small intestine and the duodenum were normal in all cases, except one in which the duodenum showed an ulcer 4 cm. below the pylorus. No changes were seen in the colon except for the perforation of a peritoneal abscess in one case. Not one instance of appendiceal lesion was noted. The gall bladder revealed no changes in seven cases, while the pancreas presented acute inflammatory changes in two cases, probably secondary to the inflammation of the posterior peritoneum. In three cases the mesentery was thickened, and the mesenteric lymph nodes were enlarged. Finally, the diaphragm was normal in all instances but two in which it was ragged, eroded, and adherent to the lung and showed inflammatory changes extending halfway through the muscle layer.

From these data one can conclude that no single route of infection can be demonstrated in pneumococcus peritonitis on the basis of clinical and pathologic findings. The upper respiratory passages in all likelihood harbor the causative organism sometimes many months before the onset of the disease. Hence the pneumococcus reaches the peritoneum by way of the blood stream. However, the exact mechanism of its passage from the capillaries into the peritoneal cavity is not yet clear. The genital origin of the infection is not borne out by operative or post-mortem examinations. The occasional lesions of the gastrointestinal tract are, as a rule, secondary to the inflammation of the peritoneum and affect principally the outer coats of the gut. The appendix is probably never the cause of the disease.

SUMMARY

A study of twenty-nine children with pneumococcus peritonitis observed in the last nineteen years is presented. The cases are divided into two groups, seventeen with nephrosis, and twelve without nephrosis.

The clinical features of the disease are briefly described.

The bacteriologic findings in the two groups differ. Pneumococcus Type I prevails in non-nephrotic cases, and Type VI, in patients with nephrosis.

Various factors affecting the prognosis are considered, the mortality in the cases with nephrosis being 76 per cent, as compared with 41 per cent in the non-nephrotic group.

From a discussion of surgical and conservative measures of treatment, one reaches the conclusion that at the present time most of the patients without nephrosis are operated upon and that little evidence can be found to show the efficacy of serotherapy alone. Sulfapyridine offers brighter therapeutic prospects.

Operative and post-mortem examination of the pelvic and abdominal organs casts no light upon the role of these organs in the pathogenesis of the disease.

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American Academy of Pediatrics

Proceedings

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO, NOVEMBER 16, 17, AND 18, 1939

Panel Discussion on Thyroid Gland in Childhood

Chairman: Anton J. Carlson, Ph.D., M.D., Chicago
Assistants: George Curtis, M.D., Columbus
Roger L. J. Kennedy, M.D., Rochester
O. P. Kimball, M.D., Cleveland
J. F. McClendon, Ph.D., Philadelphia

DR. ROGER L. J. KENNEDY.—For purposes of discussion, the other members of the Panel have agreed to accept this classification of conditions of the thyroid gland: Congenital, diffuse colloid, adenomatous without hyperthyroidism, exophthalmic, hypothyroid states including endemic cretinism, sporadic cretinism (athyreosis), infantile myxedema, juvenile myxedema, thyroiditis, and malignant disease of the thyroid. I shall discuss very briefly exophthalmic and nodular goiter.

The cause of exophthalmic goiter is not known. The distribution in the United States tends to be rather great in certain districts as compared to others. The occurrence of the disease in children is about 0.01 as frequent as in older persons. In our experience, the sex distribution is about 7:1 in favor of the females. Although the disease has been found and reported in all age periods, there is a sharp increase in the incidence after the age of 10 years.

There is no point in discussing the symptomatology except to say that any child who exhibits nervousness, exhaustion, and tachycardia should be suspected of exophthalmic goiter. In a fully developed case, the symptoms are much the same as in adults, except that cardiac irregularities are notably rare.

The disease tends to be progressive, and crises take place. Before the days of iodine, the surgical mortality rate was 9 per cent. Since then, the mortality rate has dropped to 2.5 per cent.

These glands characteristically show the change referred to as parenchymatous hypertrophy and contain only from one-fiftieth to one-twentieth as much iodine as normal.

There is some controversy regarding the treatment of exophthalmic goiter. The so-called control treatment consists of administration of iodine in large doses in addition to restriction of activities. This does not necessarily include rest in bed because many patients seem to be better if they are entering into some activity. So far as diet is concerned, there is no advantage in any particular type of diet. The only thing that should be remembered is that these patients demand a large amount of food and that they should be given enough. In the hands of some physicians, roentgen therapy has been a fairly useful adjunct in

the control of these cases, but it does offer some difficulty in the case of treated patients who come to operation. The use of sedatives is hardly necessary since the administration of iodine will usually bring about a more satisfactory state of sedation than will other drugs.

The question of surgical operation after preparation with iodine has had much discussion. Most of these patients will respond to surgical treatment. The question of a second, third, and fourth operation is one which is difficult to evaluate. Patients have been operated on in a few instances until all the thyroid has been removed and still there is a recurrence of the condition, but that situation is very rare.

The postoperative use of iodine should be stressed.

When we look at the whole situation we are still in the dark as to what causes the return to normal of a patient who has had a thyroidectomy. Why these people get well we do not know.

As to nodular disease of the thyroid gland, I wish to make a few rather emphatic remarks. In our experience all of the malignant lesions were instances of carcinoma. We have seen no sarcoma. Single nodules of the thyroid gland have proved to be malignant more frequently than benign conditions. Most of them were thought at first to be benign, but the diagnosis on histologic examination was that the lesion was malignant. It is in this field of carcinoma of the thyroid gland that there has been much argument as to whether the nodules are really malignant or benign. Most of the examples which we have encountered have been designated as papillary adenoma carcinoma. The diagnosis of cancer apparently depends upon the criteria in use by different pathologists. From our standpoint it would seem that where there has been a nodule in the thyroid gland which has been removed and in which there is evidence of malignancy and malignant involvement of the regional lymph nodes, and where we find metastatic lesions in the lung, skull, and spine, we have all that is necessary clinically to give a diagnosis of malignancy; so the pathologists may carry on the argument. From the clinical standpoint, we recognize the bulk of single nodules without any systemic symptoms as potential malignant lesions. The obvious conclusion would be that the removal of these nodules is necessary before one can decide as to their true nature, and this always means that we have to adopt the policy that the sooner they are removed, the better.

We are still looking for an instance of adenomatous goiter with hyperfunction. The terms "thyrotoxicosis" and "hyperthyroidism" seem to be needlessly general because all the cases have been instances of exophthalmic goiter, and it would seem that they should be so designated.

Adenomas occur in infants and in children with relative rarity. Most of them are probably originally colloidal adenomas because it is in the fetal adenomas that later carcinomas have been found. It has been shown that the average age at which adenomas give general symptoms is 49 years, and seldom have they been encountered before the twentieth year. The pathologic character of these tumors varies according to whether they contain encapsulated fetal or adult type of tissue. In themselves, some of these may be benign, but, without any criteria to differentiate, we have no means of knowing until these nodules have been removed.

DR. O. P. KIMBALL.—In the few minutes allotted to me I should like to give two of my experiences which emphasize the importance of thyroid function during fetal life and early childhood. Both of these observations have been given previously in my reports on goiter prophylaxis, but I feel that they should be given greater emphasis before this special group.

1. It was in 1924, while making the preliminary studies and surveys for goiter prevention in Michigan, that the problem of "congenital goiter" became a specific study. It was in a medical meeting in Houghton County where two-thirds of the school children had goiter that the physicians showed interest and anxiety over the many babies who had enlarged thyroids at birth. It seemed to be a common opinion that approximately one-half the children of the Upper Peninsula had a definite visible enlargement of the thyroid at birth. This enlargement was described by several as a ridge across the baby's throat as thick as the physician's finger. All of the physicians doing obstetrics in the Upper Peninsula volunteered to pay special attention to prophylaxis during pregnancy and to report their results each year. The yearly reports for ten years showed not a single baby with congenital goiter where the mother used iodized salt or the equivalent amount of iodine prescribed by the physician. During the same time there were families, especially those of fishermen along Lake Superior, where only bag-salt (noniodized salt) was used. Among these families, prenatal instruction by a physician was almost unknown. It followed that in this group approximately one-half the babies had congenital goiter.

This observation demonstrated the truth of our teaching as to the importance of goiter prophylaxis through pregnancy, for both the mother and the baby.

2. From 1928 to 1931 we made a study of all children in special classes in the Detroit schools. Approximately 10,000 children were examined, with one question in mind: Why is the child below the expected average mentality? Suffice it to state here that one-tenth of the cases of feeblemindedness found in this study were due to endemic goiter or, more specifically, to congenital hypothyroidism. These included cases of mongolianism, severe cretinism, and congenital hypothyroidism.[1]

Mongolianism is a congenital defect of the brain. From my clinical studies, I would say that this condition is the result of a severe deficiency of thyroid function in the mother very early in pregnancy—in about the sixth week. If this deficiency continues very long, there should be death of the fetus and miscarriage. If this deficiency is overcome within a few weeks, the fetus may mature with very little damage, except to the brain. I have seen two such cases with accurate data.

Cretinism is a severe maternal hypothyroidism coming on a little later in pregnancy and lasting over a longer period, affecting the development of the brain, circulatory system, digestive system, and osseous system. This thyroid deficiency lasts approximately from the tenth to the fifteenth week, producing the typical physical and mental cretin.

Congenital hypothyroidism is many times more common than the other two severe states, yet comparatively little has been said of these children except by our school psychologists. They first described them as a group of children characterized by a falling I.Q. On physical examination, one finds comparatively little on which to make a diagnosis. At times there is an enlarged thyroid, with distinct multiple adenoma. Again, the thyroid will not be palpable. Frequently one finds malformed teeth, especially the first permanent molars. In a few cases, this defect was striking, showing only four sharp points with practically no body to the tooth. In younger children there is considerable malformation with early decay, but nothing so striking as the first permanent molars. This can mean only one thing—a marked metabolic disturbance at the time the points of calcification were laid down. The points of calcification of the deciduous teeth are laid down from about the sixteenth week to the eighteenth week of fetal life, while those of the first permanent molars are laid down late in pregnancy, about the ninth month. Further evidence of metabolic disturbance is shown in the mal-

formation of the capillaries of the nail bed. Such capillary changes have been described fully by Jaensch and Wittneben[2] and by Hoepfner.[3] These findings, together with three years' clinical observation, helped us to reach the conclusion that the mental deficiency is the result of a lack of capillaries in the cortex, and is as much the result of the congenital hypothyroidism as the malformed nail bed or the malformed teeth. Therefore, we concluded that one-tenth of all cases of feeblemindedness in this district are due to endemic goiter, or at least to maternal hypothyroidism. Practically all of these cases could be prevented.

Dr. Kennedy just stated that the average age for the appearance of symptoms from adenomas of the thyroid is 49 years. You will often find distinct adenomas in the thyroids of children and babies. The time to prevent these is during pregnancy, and the best time to treat them is all through childhood and the growing period by keeping the iodine content of the thyroid up to normal and thereby preventing the stimulation to growth and function of the adenoma and the toxic condition seen in later life.

QUESTION.—What factors other than iodine deficiency may cause this clinical and apparent hypothyroidism?

DR. KIMBALL.—In all cases that I have studied, the final diagnosis was some pathologic condition of the thyroid preventing the metabolism of iodine to the hormone thyroxine. In one child there was a history of thyroiditis associated with mumps. The atrophy of the thyroid due to infection and inflammation made the therapy entirely ineffective; however, thyroid extract soon increased her basal rate to normal. On continuous thyroid therapy, her growth and development, as well as metabolic rate, have been normal. At the age of 8 she was the size of a 3-year-old child. Now, at the age of 16, she is her average normal in every respect.

CHAIRMAN CARLSON.—As Dr. Kimball has said, the desiderata for the pediatrician are early diagnosis before irreparable changes have taken place. Recently there has been some important work done on the possibility of assaying the thyroid hormone concentration in the blood. It does not appear in the urine; we have no way of assaying it there. As you know, the basal metabolic rate is not very good in the first year of life, and the size of the thyroid is not always a criterion of the secretory rate, so that one of the most important problems today is the measurement of rate of thyroid secretion. I shall call on Dr. George Curtis to tell us something of his work along this line.

DR. GEORGE CURTIS.—In the five minutes allotted to me, I should like to try to say three things. First, that the blood iodine is of significant value in the recognition of changes in thyroid function occurring during childhood; second, that by feeding a small amount of iodine to dairy cows we can aid in the prevention of endemic goiter in children; and third, that the use of iodine is of definite value in the prevention, as well as the management, of hypothyroidism.

The data upon which these statements will be made are published. However, it is unfortunate that there is not more time to thresh them out with this particular group. In the first place, the basal metabolic rate is not entirely satisfactory as a means of determining changes in thyroid function, principally because there are several other factors that will influence this rate.

Thyroxin, whether isolated by Kendall or synthesized outside the human body, is 65 per cent iodine. Moreover, it is clear that the thyroid gland is a principal store house for iodine and that a considerable portion of this iodine exists in the form of thyroxin. So far as I am aware, it is not certain that thyroxin circulates as such in the blood.

In 1928 we became interested in the blood iodine, and it has been found possible to assay, with a considerable degree of certainty, the activity of the human thyroid gland by determining the amount of iodine circulating within the blood. However, we must remember that this iodine content is not entirely due to circulating thyroid hormone. We would rather conclude that some of the blood iodine is in the form of broken-down thyroid hormone and that some of the remainder is from the food intake. In our early studies we did not attempt to fractionate the blood iodine because we appreciated the inadequacy of our methods and the difficulties involved, even in determining 0.0001 mg. of iodine. Nevertheless, more recent studies have shown that the blood iodine is of value in determining thyroid function, while fractionation is giving us a more definite idea of that fraction which appears to contain the thyroid hormone. However, I do not believe that we can yet conclude that this fraction of the blood iodine is "hormone iodine." We may conclude that it contains the thyroid hormone, but the chemical methods are not developed enough to conclude that any fraction is as yet the thyroid hormone.

As to the prevention of endemic goiter in children by the feeding of iodine to dairy herds, cows fed a small amount of iodine secrete a milk of increased iodine content. From analyzing that milk day after day and giving it to patients in the University Hospital, we have concluded that it is thus possible to supply an adequate amount of intake iodine. Moreover, in this manner iodine is returned to the land, to its products, and thus to other animals on the farm. It thus appears possible to affect not only man, but a number of the living things of a given region. This may be done, for example, by giving these herds feeds, or even large cakes of salt as is commonly done, in which there is an increased amount of iodine.

Finally, a further word about hypothyroidism. Hypothyroidism in children is common in those regions where goiter is endemic, as in Switzerland and central Ohio. The iodine intake in these regions is diminished. Moreover, if we analyze the milks from scattered dairies in central Ohio, we find a striking variation in the iodine content. In some, the milk iodine is definitely increased, whereas it is found that those herds received a feeding supplement. Other dairy herds without this supplement may even have a decreased iodine content in their milk. Because of this, in the management of hypothyroidism in children in this region, we give them first a small amount of iodine, 10 mg. a day, for a few days in order to replete the reserve which may have been depleted during the previous period of insufficient iodine intake. We have had encouraging results following such management.

CHAIRMAN CARLSON.—It has taken the western world about five or six hundred years to work out the iodine problem in connection with the thyroid gland. It is astonishing how near we were to this and then forgot it for one hundred years. You may think that iodine is the whole story and that all you have to do is to paint these patients with iodine. This is not true. Iodine is not the whole story, and the next speaker probably has done more than anyone else on this problem in his survey. He informs me that recently he has also taken up the same problem as Dr. Curtis, namely, the possibility of developing a real assay method for the level of thyroid function in children.

DR. J. F. McCLENDON.—At present the basal metabolic rate is the only practical method for determination of thyroid function in a patient. However, for twenty years I have been refining a technique in the hopes that we could determine by chemical means the thyroid function. I will correlate it with the

basal metabolic rate, and you can judge for yourselves whether this is thyroid hormone iodine that we are determining in the blood.

The normal basal metabolic rate is considered to be somewhere between 35 and 40 calories per square meter per hour. We have to express it that way to get away from age and sex. I have determined the basal metabolic rate every day for a year in some patients, thus determining its variations. The thyroid hormone iodine in the blood was determined in about 250 patients. If we now plot a curve (starting with a cretin), it would be 26 calories per square meter per hour and on up to 56 calories per square meter per hour, and the normal values will be somewhere in the 35-40 region, depending upon age and sex. If we plot the hormone iodine in the blood, we will go from 0 at the lower border to 10 at the top. At the value of 26 calories per square meter per hour, we have an average of 2 μg per 100 c.c. for hormone iodine; as we approach 46 calories, we have a value of 6. One of my friends disagreed with this method; he said we should take people with the same hormone iodine content and determine their basal metabolic rate. So we have done that. We find a little different curve. The shape of the curve is different when we do the hormone iodine first and then determine the basal metabolic rate on all the people who have the same hormone iodine; the two curves, however, are very close together. If there were no correlation, they would be at right angles. Therefore, although I have not calculated the exact correlation coefficient (we are still doing the determinations and have done only about 250), I believe from what we have here that the more determinations we get, the closer these curves will come together. Therefore, there is probably a close correlation between the hormone iodine in the blood and the basal metabolic rate.

CHAIRMAN CARLSON.—Despite the fact that at the present time we seem to know more about the thyroid gland and its function and its hormones than we do about any other of the endocrine glands, we have not here the complexity of the pituitary, the adrenals, or the pancreas. The thyroid apparently is composed of only one hormone. Despite all that, the story of the thyroid gland in childhood and adulthood is by no means clear. If I should say anything of importance to this group at this time on the basis of my own experience and knowledge of the literature, it would be this: The prime desiderata of today are better methods of diagnosing incipient or slight degrees of hyperthyroidism. As Dr. Kennedy said, hyperthyroidism is rare in childhood, but it can be handled by the same technique and the same approach that we are using in the adult. Hypothyroidism in the adult is not serious except during pregnancy, and then from the point of view of the coming child. The seriousness of slight hypothyroidism in early infancy and during prenatal life, however, is that very early irreversible changes occur which escape diagnosis and the therapy that is available. Therefore, we have the disappointing results of thyroid therapy when the conditions are discovered later. I confess I am tremendously puzzled that the extensive endemic goiters, and particularly the adolescent goiter in girls, are not accompanied by gross symptoms of cretinism more frequently than they are. It means that there must be some irreducible low level of thyroid hormone production under which we can carry on fairly well.

I do not think any internist or any first-class pediatrician can be blamed seriously for not being able to put his or her finger on incipient hypothyroidism in early infancy. We just do not have the means.

I should like to ask my colleagues, particularly Dr. Kimball, how this type of thyroid enlargement indicates hyperthyroidism even though you cannot measure it. What outside agent is there that controls the thyroid? What is it that con-

trols the rate of activity of the thyroid gland? Some workers have said that there is a hormone from the pituitary which is thyrotropic, which stimulates hyperplasia and hypersecretion. I want to give a note of warning here. The fact that this occurs in the rabbit, possibly in the rat and guinea pig—we are not certain of it in the dog—indicates that we cannot be certain until we have definite data in man in this respect. There is no practical utilization of this. The hormone from the pituitary is not available so far as I know. We have no certain way of stimulating increased production of that hormone of the pituitary so far as I know. That is one of the difficult things because the line of investigation started many years ago on the theory that the level of output of the thyroid hormone is controlled by the central nervous system, but this has not been substantiated. That was a favorite theory among internists for years. It has not been substantiated except in this possibility, that there is a nerve from the hypothalamus to a lobe of the pituitary; this lobe is in the part of the gland which produces thyrotropic hormone. Now, what controls that activity of nerves from the hypothalamus to the pituitary, we do not know.

DR. KIMBALL.—What other factors cause this clinical and apparent hypothyroidism? I have seen that many times and have studied many patients. You build them up to normal with all the thyroid they can take. I have given them iodine too, and still there is a low basal metabolic rate and all the symptoms of clinical hypothyroidism. I have found many of them associated with low vitamin intake. I am sure that in some way the thyroid function is sustained by the pituitary, and that is the part that I cannot answer. I have seen that problem frequently and know exactly what Dr. Carlson means, and I still cannot tell him why there is clinical hypothyroidism. There are a few that I have seen. I have the authority of the pathologist to tell you that occasionally the thyroid gland, for some reason, is entirely too small or atrophic, or, for reasons we cannot understand, the thyroid cells will not metabolize iodine and will not react normally. It is for some reason other than chemical reaction. The cells themselves cannot use it; it may be tied up with the pituitary gland, and it may be due to abnormal vitamin intake.

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NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO, NOVEMBER 16, 17, AND 18, 1939

Round Table Discussion on Convulsions

Chairman: M. G. Peterman, M.D., Milwaukee
Secretary: J. E. Dyson, M.D., Des Moines

Convulsions

M. G. Peterman, M.D., Milwaukee, Wis.

Perhaps it would be well to begin the discussion of this subject with a few definitions and explanations. The Latin word convulsion means motor contraction. My definition is this: "A convulsion consists of a series of involuntary contractions of a group or several groups of muscles, usually associated with a loss of consciousness."[1] At the 1939 combined meeting of the Section on Convulsive Disorders of the American Psychiatric Society and the American Chapter of the International League Against Epilepsy, Temple Fay said: "A typical major convulsion is a normal mass reaction of defense to protect the individual against threatened or actual degree of cerebral anoxia. In brief and common language, it appears to me to be a healthy and necessary physical 'workout' required to overcome a threatened failure in cerebral circulation."[2] In reply, Penfield said: "I am amazed by the suggestion that an epileptic seizure is in any sense a beneficial occurrence. I can't understand the point of view that would suggest that it protects the brain against anoxia. Epileptic seizure, when it occurs, produces an increase of blood flow through the brain, but it does so because it has produced an overwhelming amount of local carbon dioxide. The brain, even in spite of increased blood flow, is in the condition of anoxemin because of this seizure. I can't see any excuse for suggesting that it serves any beneficial purpose whatever. It results either in temporary paralysis of the nerve cells involved or in a very long-lasting one. I don't see any reason, excepting on the basis of philosophical flight, to suggest that it is beneficial or that it is a reflex."[3]

Since the "brain specialists" cannot agree upon a definition of a convulsion nor upon the actual cause, perhaps the pediatrists should not have the temerity to try. I would, however, agree with Penfield that a convulsion is a violent and abnormal reaction to a stimulus and that it is an end reaction and a harmful one. Anoxemin of the brain is not always essential to precipitate a convulsion. It probably is not responsible for the convulsions of tetany, tetanus, or acute poisoning, namely, for those convulsions which are acquired and are precipitated suddenly by some sudden change in blood chemistry. Lennox says: "The fundamental cause of seizures must be some disturbance in the physiology or chemistry of the cerebral ganglion cells which under appropriate stimulus renders the cell abnormal. This abnormality may be closely linked with what we glibly call heredity."[4] There are many types of convulsions in childhood, and the different characteristics may be demonstrated in the moving pictures.[5] The distinctive types are the convulsions of petit mal epilepsy, of grand mal epilepsy, of tetany or spasmophilia, and of tetanus. There may be others. Except for the convulsions produced by poisons such as strychnine or in uremia, the child who frequently reacts to a stimulus with a convulsion must have some inherited constitutional defect.

There is also a typical response pattern in many convulsive disorders which is well known clinically. For instance, the patient with idiopathic or essential epilepsy has an onset of convulsions, for example, in his eighth year. If the disease is untreated, the seizures tend to increase progressively in frequency and in severity. The infant with cerebral birth trauma usually has his first seizure within the first month of life, and the number of seizures tends to gradually decrease. The infant with tetany has a seizure only when it is stimulated or aggravated or when he develops an acute infection. Some children with a constitutionally low threshold for convulsions will have a seizure only when the body temperature reaches a certain high point. The evidence for heredity and an inherited constitutional defect in epilepsy has been substantiated by the electroencephalogram. Lennox reported that "out of thirty cases in which we have been able to make electroencephalographic records of both parents, there was no instance in which both parents were undoubtedly normal with regard to their record. . . . We separated our group of patients into those of the so-called essential group and the so-called symptomatic group, and we found the symptomatic group, that is, those in whom there was apparently some injury of the brain in the first seizure, had 60 per cent as many near-relatives with epilepsy as the so-called essential group; that is, the symptomatic group had three times as many near-relatives with epilepsy as in the general population, whereas the essential group has five times as many."[6]

In this connection it is interesting to note that the neurologists have tried to replace the word "epilepsy" with "convulsive state." Yet, when Cobb refers to this syndrome, he says, ". . . Epilepsy was perhaps rather usually precipitated and I am using the word 'epilepsy' as meaning the disorder as we know it clinically."[7]

I have seen no case of major convulsions which was due to hypoglycemia. The person who has major convulsions whenever his blood sugar reaches an abnormally low level has a constitutionally low convulsion threshold and may be a potential epileptic.[5] Harris says, "There apparently are differences between the convulsions of hypoglycemic shock and epileptic seizures. The various motor phenomena observed in hypoglycemic shock simulate movements usually associated with disease of the basal ganglia and brain stem, and the epileptiform seizures have a different sequence of events than those classically occurring in true epileptic seizures."[8] Woods stated, "For the present, hypoparathyroidism and hypoglycemia should not be included as the cause of epilepsy. Disturbances of consciousness and of motor coordination based upon these causes would better be described as symptoms of those derangements, respectively."[9]

I have listed[5] the causes of, or perhaps the etiological factors which precipitate, convulsions. This classification was submitted as a working basis for the further study of the convulsive state. You are all familiar with the fact that the child is subject to certain hazards or diseases in certain age periods. These hazards or diseases are particularly prone to lower the threshold or to precipitate convulsions. Perhaps the classification may be simplified or generalized to divide the causes of convulsions into the following:

Organic	1. Congenital or developmental cerebral anomalies 2. Antenatal, natal, or postnatal cerebral injuries 3. Antenatal, natal, or postnatal infections or poisonings and the residues thereof 4. Idiopathic epilepsy
Nonorganic	1. Chemical injuries or acute poisonings

Note that idiopathic epilepsy is listed under the organic diseases. In view of the consistent electroencephalographic findings in epileptics and in their parents, it may become necessary to modify my definition of idiopathic epilepsy. This

disease is "a chronic disease of the central nervous system characterized by periodically recurring convulsions, lapses, or abnormal mental states which occur in an individual with a constitutional inferiority or personality defect but with no demonstrable pathologic lesion."[10] It is difficult to understand why the epileptic child with his inherited nervous system defect does not have convulsions until his disease has developed. In my series he passes through the various potential convulsive diseases of infancy with no convulsions. Only 5 per cent of my epileptic patients have had convulsions in infancy preceding the onset of epilepsy. This incidence is no higher than in a control group of nonepileptic children.[11]

The diagnosis of the causes of convulsions still rests mainly on the history. Every effort must be made to obtain all the information possible as to the type or character, duration, and frequency of the seizures and of the associated phenomena. The family, birth, and past histories are of great value, particularly in a study of chronic convulsions.

Treatment.—If convulsions are due to fever, reduce the fever with cool packs. Do not use hot baths unless there is a subnormal temperature. Cool enemas may be used. Chloroform may be administered. Chloroform is better than opium, as the latter depresses the respiratory center and inhibits peristalsis. In place of chloroform, a 50 per cent solution of magnesium sulfate may be given as an enema or by mouth. A 20 per cent solution may be given intramuscularly, even intravenously if given slowly. Phenobarbital is too slow in action for immediate effect. Spinal puncture is always indicated to rule out meningitis and other diseases. The convulsions of tetany require calcium; those of tetanus require avertin.[13] Status convulsivus usually is fatal unless treated with chloroform or magnesium sulfate. In chronic convulsions as the result of brain injury, phenobarbital may be given over a long time. In idiopathic epilepsy phenobarbital may be used as a specific for therapeutic trial. If the patient does not respond, he probably has an organic lesion. Phenobarbital is only a symptomatic treatment. We should treat epilepsy by diet (high fat), rest, and regulation. No drug has any effect upon petit mal in children. Nearly one-half of the cases of epilepsy start as petit mal. Fasting and ketogenic diet will control one-half of the petit mal cases.

DISCUSSION

DR. T. O. ELTERICH, Pittsburgh.—Will you please give the dosage of magnesium sulfate?

CHAIRMAN PETERMAN.—Fifty per cent magnesium sulfate solution, 1 ounce is given orally or rectally to children under 1 year; 2 ounces to children from 1 to 5 years; 4 ounces to children from 5 to 10 years. Twenty-five per cent may be given intramuscularly, 5 c.c. up to 1 year; 10 c.c. up to 5 years; from 10 to 15 c.c. up to 10 years. Twenty to 25 per cent solution may be given intravenously, from 1 to 2 c.c. under 1 year; from 2 to 3 c.c. up to 5 years; from 3 to 5 c.c. up to 10 years. It should be given very slowly.

DR. OTTO GROB, Detroit.—Have you had any sloughs?

CHAIRMAN PETERMAN.—It is possible but not usual.

DR. C. C. STEWART, Hanover, N. H.—Did you say that epilepsy occurred in inferiors?

CHAIRMAN PETERMAN.—Epileptics have inherited a constitutional inferiority. Their reaction to environment and situations is abnormal. Most psychologists doubt that there is any difference in the epileptic person. The epileptic child very early is more difficult to get along with. He has peculiar food likes. He prefers adult

company or to be alone. Frequently the epileptic persons are precocious children. L. Pierce Clark said that the epileptic had a constitutional inferiority. A prolonged period of apnea or delayed breathing in the newborn infant must do a lot of damage. A number of babies who have cerebral anoxemia will have injury of the cortex, which may be the cause of convulsions. We may call them epileptics later on, not knowing about the brain injury. And, too, we should never minimize the slightest fall. The child deserves careful observation afterward. Children should be kept quiet at least twelve hours after convulsions.

DR. HARMON TREMAINE, Boise.—May epileptic convulsions in a child past 6 years of age be classed as a form of eclampsia?

CHAIRMAN PETERMAN.—The Germans use the word eclampsia to include hysteroepilepsy and many kinds of convulsions. Hysteroepilepsy and idiopathic epilepsy are often found in the same patient.

DR. TREMAINE.—Even if he does not actually lose consciousness, as in a hysteria?

CHAIRMAN PETERMAN.—The child does not always lose consciousness in epileptic seizures. Patients with petit mal who have seizures when they are scolded must have a psychic trigger mechanism.

DR. S. H. ASHMUN, Dayton.—What is pyknolepsy?

CHAIRMAN PETERMAN.—Pyknolepsy is a mild petit mal on the electroencephalogram.

DR. E. A. WAGNER, Cincinnati.—What is narcolepsy?

CHAIRMAN PETERMAN.—It is an uncontrollable desire to sleep which recurs irregularly, even under excitement. It is not common in children.

DR. W. F. MATTHEWS, Montclair, N. J.—Does pyknolepsy clear up at puberty?

CHAIRMAN PETERMAN.—Like petit mal, it may clear up at puberty.

DR. GROB.—Is there any relation to epilepsy?

CHAIRMAN PETERMAN.—I believe they are identical.

DR. ASHMUN.—Would you care to say something about pyknolepsy and the nodding type or salaam spasm and whether recent studies have shed new light upon these two types of epilepsy? Dr. Kramer of Akron and I have both observed adolescent girls who have fainted on fast days, apparently as a result of hypoglycemia. Might not these be cases rather of momentary convulsions easily mistaken for a faint?

CHAIRMAN PETERMAN.—I have seen more girls than boys who fainted in church after prolonged fasts.

DR. M. B. BROOKS, Los Angeles.—Is it possible to recognize pre-epilepsy, as in a sleepwalker?

CHAIRMAN PETERMAN.—Case report * * * * * * * * * * * * * * * * one child with nightmares regularly at 9:00 P.M. after falling asleep. They began with crying and uncontrollable delirium. Three months later he had seizures at the same time and in place of the nightmares.

DR. TREMAINE.—Please explain the electroencephalogram.

CHAIRMAN PETERMAN.—The electroencephalogram registers a difference in potential of different areas in the brain. There are certain waves in sleep and waking. In the epileptic there are various waves, according to the type. The waves are fast and of high voltage in grand mal. In petit mal there are alternating and slow waves.

CHAIRMAN PETERMAN.—Dr. Kennedy, would you please tell us of your experience with the electroencephalogram and its place in diagnosis?

DR. R. L. J. KENNEDY, Rochester.—We use it as an aid to diagnosis. We have found a very high correlation between the diagnosis as arrived at by history and physical examination and the electroencephalogic findings.

DR. A. T. MARTIN, New York.—Please report on your series of eight patients under 8 years with idiopathic epilepsy.

CHAIRMAN PETERMAN.—They were patients observed after five or ten years who had had seizures the first six months of life and had progressed. They still have seizures, but they are on a diet and phenobarbital.

DR. MARTIN.—Do you think they should all have encephalograms?

CHAIRMAN PETERMAN.—If you have someone to interpret encephalograms, they should be made on all patients with chronic convulsions. You can then give a better diagnosis and prognosis. One might find a porencephal or a tumor in a case diagnosed as epilepsy.

DR. J. C. OVERALL, Nashville.—What anesthetic do you use for encephalograms?

CHAIRMAN PETERMAN.—Phenobarbital, avertin, and morphine.

DR. MARTIN.—I had an 8-month-old baby with convulsions on whom we made an encephalogram and found no defect. The convulsions then stopped for six months, only to return. They were controlled on dilantin 0.1 Gm. three times a day. How about using dilantin?

CHAIRMAN PETERMAN.—Frisch in Vienna uses air injection into the subdural space as treatment, but I have not felt that encephalograms gave any benefit. I have used dilantin, 1.5 gr. two to three times a day, to replace 1.5 gr. phenobarbital in children. Most parents discontinued dilantin within three months and returned to phenobarbital. I have only three patients on dilantin from choice. I have found that dilantin does not control patients if phenobarbital did not. It might be used if phenobarbital stimulates, rather than depresses, the patient. I know that phenobarbital sometimes seems to stimulate chronic encephalitis. Dr. Kennedy, could you get along without dilantin?

DR. KENNEDY.—We have seen a few cases in which dilantin seemed to control attacks when the ketogenic diet and phenobarbital failed to do so. We have found that frequently phenobarbital is not prescribed in sufficiently large doses and its administration is not continued without interruption. The dose may be increased at intervals of a month or so until either the attacks are controlled or the physiologic dose is exceeded. If the latter occurs, as indicated by dullness and grogginess on the part of the patient, the dose may be reduced slightly and then maintained indefinitely at that level. For a patient aged from 10 or 12 years, 0.75 gr. twice daily is not a large dose. One or 1.5 gr. twice or three times daily would be more nearly the desirable dose if results did not follow the administration of the smaller amount.

DR. C. H. SMITH, New York.—Did you ever see dilantin increase convulsions?

CHAIRMAN PETERMAN.—I have had mothers report an increase in symptoms.

DR. SMITH.—How much phenobarbital would you give a day?

CHAIRMAN PETERMAN.—I have given as high as 8 gr. phenobarbital a day.

DR. L. J. SCHERMERHORN, Grand Rapids.—Do you think phenobarbital is harmless over a long time?

CHAIRMAN PETERMAN.—Yes, it is harmless. It can only cause a rash.

DR. SCHERMERHORN.—How about changes in the brain?

CHAIRMAN PETERMAN.—There is no danger. I have given a 5-year-old patient 6 gr. a day for three years. I have always avoided bromides.

DR. J. K. EVERHART, Pittsburgh.—You recommend 0.75 gr. phenobarbital b. i. d.? If you did not succeed, then how much?

CHAIRMAN PETERMAN.—From 1 to 1.5 gr. t. i. d.

DR. SMITH.—The routine orders for convulsions on the Children's Medical Service of Bellevue Hospital may interest you.

I. Patient admitted during a convulsion:

a. Chloroform, 1 or 2 drops at a time on mask, with plenty of air.
b. If twitching persists, sodium amytal intraveneously very slowly until patient relaxes. (Maximum dose, 0.04 gr. per pound.)

II. As soon as convulsion ceases:

a. Magnesium sulfate, 25 per cent, from 5 to 10 c.c. intramuscularly
b. Lumbar puncture for diagnosis and relief of pressure
c. Soapsuds enema
d. One-half hour after enema, sodium bromide 0.75 gr. per pound, and chloral hydrate, 0.1 gr. per pound by rectum, to be retained
e. If temperature is 104° F. or more, aspirin, 0.1 gr. per pound by mouth as soon as patient can swallow
f. Calomel 0.1 gr. every 15 minutes for six to eight doses. In morning, milk of magnesia, 30 c.c.
g. Laxative each night thereafter
h. Sodium bromide, 0.125 to 0.25 gr. per pound every six hours for forty-eight hours.

III. Patient admitted with definite history or recent convulsion is treated as in II. It is physician's duty to prevent second convulsion, in which there may be cerebral hemorrhage or other accident.

IV. Chronic epileptics, after an attack:

a. Enema, laxative
b. Bromide by mouth, one or two doses
c. Phenobarbital, 0.25 to 1 grain t. i. d.

DR. OVERALL.—How long have you kept chilldren on a ketogenic diet?

CHAIRMAN PETERMAN.—Twelve years. However, in children we must give 1 Gm. of protein per pound each day.

DR. J. W. BRITTON, Anniston, Ala.—Do you have any trouble keeping up the ketogenic diet at home?

CHAIRMAN PETERMAN.—Much less than with adults. The secret is a good dietician who can make the diet attractive.

DR. OVERALL.—What do you do about ketogenic diets in the face of acute infections?

CHAIRMAN PETERMAN.—When there is fever, increase the carbohydrates.

DR. GROB.—How long do you keep patients on the ketogenic diet?

CHAIRMAN PETERMAN.—I keep them on the ketogenic diet two years, until they are free from convulsions, and on phenobarbital indefinitely. Later on, I keep them on a diet without sugar and as high a fat content as possible.

DR. OVERALL.—How do you explain convulsions in patients with low blood sugar over a period of years?

CHAIRMAN PETERMAN.—I have not seen them. They have been diagnosed by the exponents of hypoglycemic convulsions or hyperinsulinism.

DR. OVERALL.—How about the child when a mother had low blood sugar?

CHAIRMAN PETERMAN.—Probably a low convulsion threshold. There are distinct differences between convulsive seizures and the shock of hypoglycemia. I can illustrate these differences well in the moving pictures of both. The motor phenomena in hypoglycemia shock are those associated with brain stem and basal ganglial disturbances. Andrew Woods says that "hypoparathyroidism and hypoglycemia should not be included as the cause of epilepsy. Disturbances of consciousness and of motor coordination based upon these causes would better be described as symptoms of those derangements, respectively." I have never been able to establish hypoglycemia as a cause of recurring convulsions.

DR. L. A. SMITH, Ogden, Utah.—Have you seen epileptic-like seizures from pinworms?

CHAIRMAN PETERMAN.—No. It may be like cutting teeth; it may be the trigger causing convulsions in a patient with a low threshold. The setup must be there.

DR. GROB.—Will you discuss tetany of the newborn infant?

CHAIRMAN PETERMAN.—I feel that there is enough evidence that babies are born with low calcium, not necessarily high phosphorus, to say that tetany of the newborn infant exists. There is probably a hypoparathyroidism. Chvostek and Trousseau signs may not be present. You may stop seizures with adequate calcium and the use of parathyroid extract.

DR. R. C. GOOLSBY, JR., Macon.—Is tetany related to epilepsy?

CHAIRMAN PETERMAN.—No, babies who have spasmophilia do not develop epilepsy.

DR. B. A. MAZUR, Fargo, N. D.—Have you used the pitressin test?

CHAIRMAN PETERMAN.—Water balance has something to do with convulsions. No epileptic person should take large amounts of water. Deep breathing alklosis is not diagnostic and will not always cause seizures, but the so-called pitressin test is of no value.

DR. T. J. McELHENNEY, Austin.—Is there any reason why we should not use mandelic acid to produce ketosis and thereby replace the ketogenic diet?

CHAIRMAN PETERMAN.—Mandelic acid has been used as a substitute for the ketogenic diet to produce a similar effect upon the urine. I have tried mandelic acid on epileptic patients and have found it to have no effect whatever on convulsions. It is well known that mandelic acid is excreted unchanged in the urine. It is not conjugated or metabolized and, therefore, does not produce the ketosis or B-hydroxy-butyric acid which is the aim of the diet. I have demonstrated that the acidification produced with ammonium chloride or with an organic acid has no effect upon the convulsions of epilepsy.

DR. R. E. JENNINGS, East Orange, N. J.—Is there any good evidence of food allergy as the cause of epilepsy, and what is the rationale for the evacuation of the bowels?

CHAIRMAN PETERMAN.—The rationale is older than Hippocrates. Epileptic children may have food idiosyncrasies such as sausage, peanuts, and hot dogs. The mother will tell you that two or three days before the bowels had not moved well.

DR. GROB.—What about the future of these epileptic children—institutions?

CHAIRMAN PETERMAN.—Yes, institutions.

DR. MARTIN.—What do you advise the epileptic person about marrying and having children?

CHAIRMAN PETERMAN.—Epileptics may get married, but they should be sterilized first.

DR. MARTIN.—How should one advise if there is no clinical epilepsy and yet the electroencephalogram pattern is positive for epilepsy?

CHAIRMAN PETERMAN.—If the pattern is positive for epilepsy, there is a 20 per cent chance of the progeny having epilepsy.

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NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO, NOVEMBER 16, 17, AND 18, 1939

Round Table Discussion on Sucking Habits and Deformities of Dental Arches

Chairman: Harold J. Noyes, D.D.S., M.D., Chicago
Assistant: William S. Langford, M.D., New York
Secretary: Howard J. Morrison, M.D., Savannah, Ga.

CHAIRMAN NOYES.—How long the pendulum of professional and lay thought has been swinging to and fro with respect to sucking habits, considered as an etiological factor in deformities of the dental arches, I do not know. The changing complexion of our thought and judgment with respect to this subject is significant chiefly because of the emphasis which it places upon conservative opinion.

It has taken almost one hundred years to complete the last somersault in our mental gymnastics in this problem. For approximately three-quarters of a century the persistent exposition of a cause-and-effect relation between sucking habits and malocclusion gradually impressed the dentist, orthodontist, pediatrician, and parent that these habits were practically a certain cause of facial deformity. The concept found its way into dental textbooks and lay literature with inevitable repercussions upon the pediatrician, for the habits are difficult to combat. There was some solace in the opposition which the child psychologist offered to forceful breaking of the habits, and, when the objective approach contributed by studies of normal children indicated that a majority of those who discarded the habit before the end of the first dentitional period suffered no disturbance in the permanent dentition, the pediatrician heaved a sigh of relief and felt secure in giving advice that we forget the entire matter.

Unfortunately, we cannot dismiss the problem as casually as present indications of the pendulum would indicate. As an orthodontist I cannot be satisfied nor can you as pediatricians be content with giving advice on the basis of generalities. We might as well revert to the advice of our grandmothers that most children who have measles get well and do not have the disease again; therefore, pay no more attention to it. It seems to me that a more intelligent approach to the problem lies in a consideration of the relation which thumb- and finger-sucking bear to the fabric of etiology of malocclusion and the significance of the habits in the light of the psychiatric background of the child. It is my province in this round table to discuss only the former.

The physical conformation of face, jaws, and dental arches is attained by the interaction of very complex forces which, from a physiologic standpoint, may be roughly grouped under the headings of heredity, growth, development, and function. Since few, if any, human beings are able to escape the vicissitudes of hereditary circumstance and adverse environmental conditions, our own faces, as well as the faces of the children we observe, represent the end result of the action of the forces mentioned as they are compromised by detrimental influences which may likewise be classified under general headings of malnutrition, disease, pressure, and trauma (Fig. 1).

The face we observe at any one examination is a cross-section picture of the action and interaction of the multitude of influences falling under the above classification, as they affect and are, in turn, affected by the structural biologic mechanism of the facial architecture. Because the detrimental effects of the habits of finger- and thumb-sucking fall essentially within the category of pressure influences, we are concerned primarily with the mechanism of normal functional and facial form.

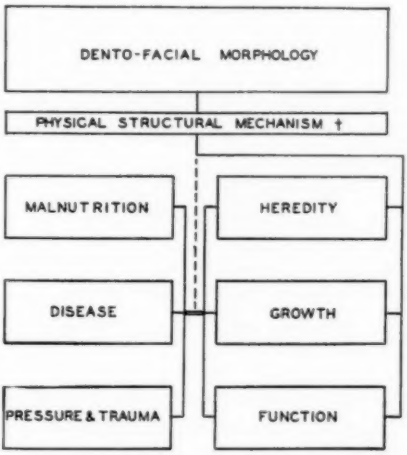


Fig. 1.—A chart indicating the normal factors of heredity, growth, and function as influenced by the abnormal factors of malnutrition, disease, pressure, and trauma affecting the dentofacial morphology or dental architecture through the physical [illegible]

We may for convenience begin with the teeth, which, contrary to common opinion, are extremely mobile units in this mechanism. Their position, once their form and location in the jaws is determined by heredity, growth, and development, is maintained by the myriad fibers of the peridental membrane which, calcified on the root side into cementum of the tooth and on the alveolar aspect into the spicules of alveolar bone, transmit pressures to which their crowns are subjected to the bone that holds them. The alveolar bone is peculiarly responsive to these pressures changing its architecture and, thereby, the tooth position to accommodate the dental units to their environment. As little as 50 Gm. of pressure, operating continuously over a period of twelve hours, will produce a measurable displacement; and the mechanical pressures of an orthodontic appliance will move teeth at the rate of one or more millimeters a month. The teeth are not held in the substance of the jaws like a post cemented in a posthole, but rather they are swung like a hammock in a specialized bone structure which responds to inherent physiologic, as well as extraneous, pressures.

The conformity of the teeth also affects their position as they make contact with their neighbors in the same dental arch and their antagonists in the complementary denture (Fig. 2). As the rounded surfaces of teeth from maxilla and mandible approach one another in the process of eruption, the fraction of a millimeter may at one time determine whether they fall in normal or abnormal position. Once their fate has been determined, functional forces of occlusion may be

†By this term is meant the interaction and exchange of influence of the hard and soft tissues of the oral and adjacent structures.

beneficial or detrimental in assisting them in maintaining a normal relation or locking them in malocclusion. Through the same mechanism, the absence of a dental unit or its abnormal position has effect upon other dental units through the contact relationship of teeth in the same arch and the opposing denture through the occlusal interlocking of their surfaces when the jaws are closed. In this way a defect in one region may have a remote effect.

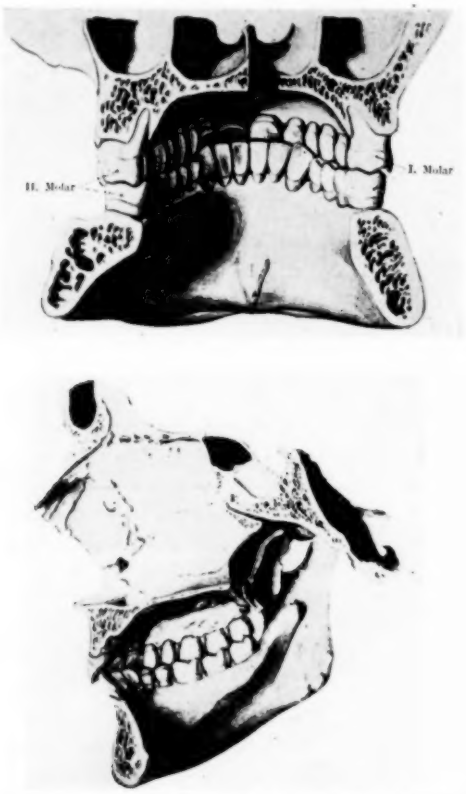


Fig. 2.—An illustration of the relationship of dental units showing the importance of integrity of the dental arches and their mesiodistal and buccolingual interdigitation. The reciprocal relationship of the teeth within and between the arches is apparent. (Reproduction from H. Sicher and J. Tandler, Anatomie für Zahnarzte, Berlin, 1928, Julius Springer.)

The axial relation of the teeth is important also because of its distribution of the forces generated in mastication. A child may use from 50 to 150 pounds of pressure in mastication. If the teeth were so placed that their axes were vertical, as the mandible is carried to the maxillae the interaction of forces would be equal and opposite. But there is an anterior inclination to the dental axis, varying somewhat according to racial pattern, which leaves a vector of the masticatory force in an anterior direction (Fig. 3). This mechanical factor tends to drive both dentures forward in proportion to the degree of inclination and the power of muscular contraction.

As we come to appreciate the ease with which the teeth may be shifted in their bony support, we are in a better position to understand the importance of

the soft tissue pressures which affect the integrity of the dental arches. The tongue within and the facial musculature externally exert a very significant influence upon arch form. Paramount from the standpoint of the denture is the buccinator muscle. From behind the last molar tooth at the pterygomandibular

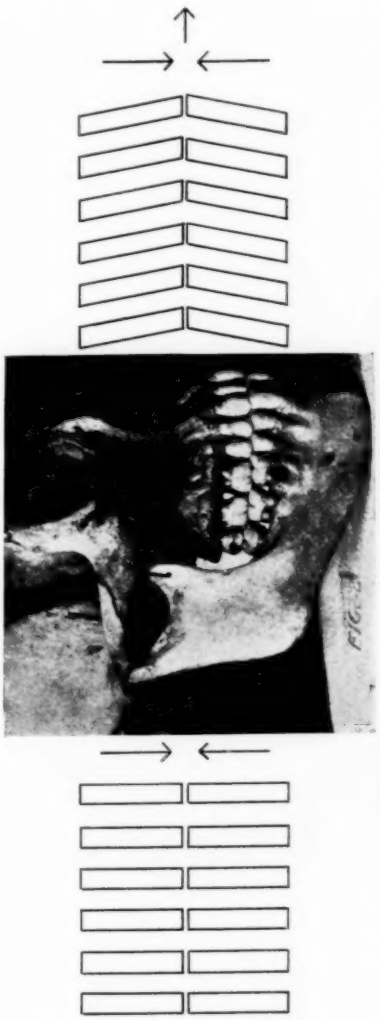
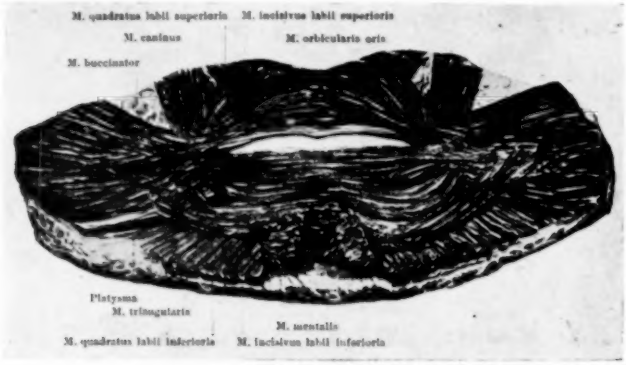


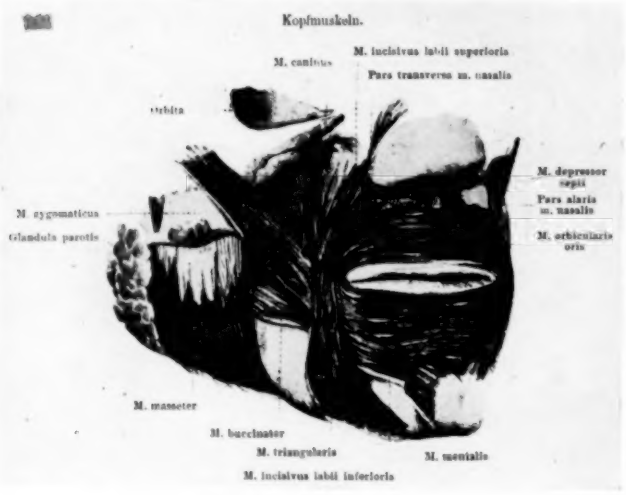
Fig. 3.—A diagrammatic representation of the reciprocal forces in mastication. *Left*, a vertical dental axial arrangement in which the entire force of the impact of the mandibular denture is absorbed by maxillary support; *right*, the anterior vector of force due to the axial inclination of the dental units is indicated; and *center*, axial inclination of the teeth illustrated in a human skull.

raphe the fibers of the buccinator mingle with those from maxilla and mandible and, as they meet anteriorly, comprise much of the orbicularis oris. The medial fibers decussate at the angle of the mouth, those from below going to the upper, and those from above to the lower, lip. In this fashion a band of musculature supports the teeth and alveolar process externally (Fig. 4*A*). The contraction of the buccinator compresses the denture and, through the decussation of the medial strands accentuated by the risorius muscles, tends to close the lips.

The insertion of the facial muscles at the angle of the mouth, particularly the caninus and zygomaticus from above, whose fibers insert in the body of the lower lip, and the triangularis below with portions which reach the upper lip, not only supplies bulk to this muscular mass but relieves the constricting band at the



A.



B.

Fig. 4.—Illustrations of the supporting facial musculature about the dental arches. *A*, Dissection of the orbicularis viewed from within, showing the decussation of the medial fibers of the buccinator and their contribution to the lips.

B, Dissection at the angle of the mouth, showing the insertion of the triangularis in the upper lip and the caninus and zygomaticus in the lower lip. The confining effect of this muscular complex is apparent. (Reproductions from W. Spalteholz, Handatlas der Anatomie des Menschen, Vol. II, Leipzig, 1922, S. Hirzel.)

cuspid area of the dental arch (Fig. 4*B*). Perhaps through this influence in part, and because of the wider surface bearing offered by the incisors, the constricting pressure tends to conform the dental arch into the arcs of two circles of dissimilar

radii, one upon the lateral segments and one in the anterior cuspid-to-cuspid region. The mask of the facial musculature comprised of these and the remaining muscles which mingle with those mentioned exerts the principal restraining influence upon the denture.

The anchorage of this musculature is not confined to the facial bony framework, for, from the distal extremity of the pterygomandibular raphe, fibers of the superior constrictor of the pharynx pass upward, medially, and posteriorly to be inserted at the pharyngeal tubercle of the occipital bone anchoring the buccinator mechanism to the base of the cranium (Fig. 5). It is because of this occipital attachment that the orthodontist stresses the importance of lip function. Indeed the slogan for the patient who suffers from protrusion of the anterior teeth is "Keep your mouth shut."

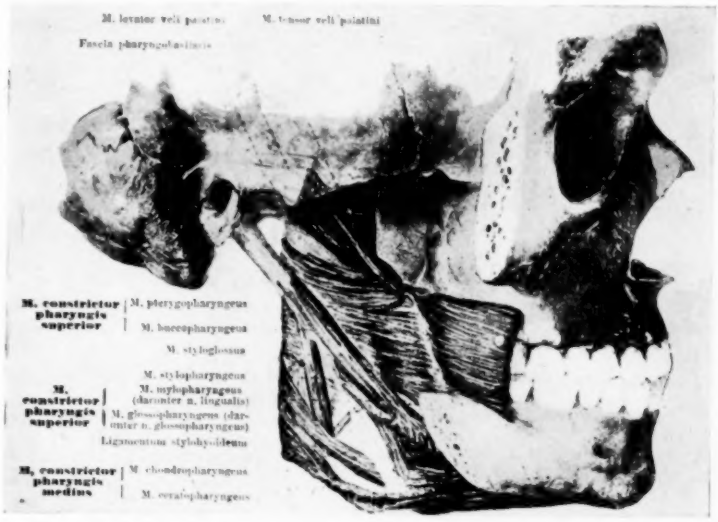
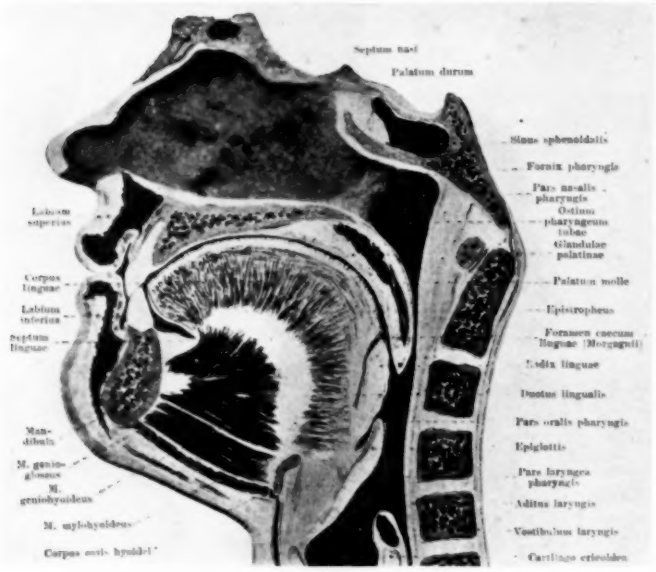


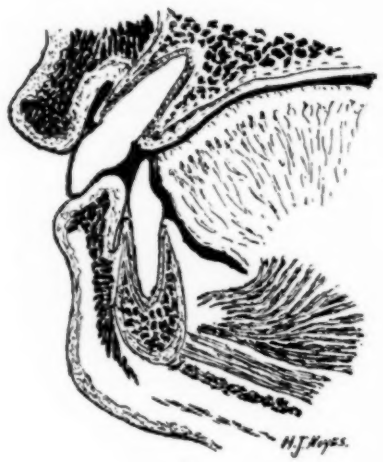
Fig. 5.—An illustration of the posterior anchorage of the buccinator mechanism through the pterygomandibular raphe and the superior constrictor of the pharynx ascending to the base of the occipital bone. (Reproduction from W. Spalteholz, Handatlas der Anatomie des Menschen, Vol. III, Leipzig, 1922, S. Hirzel.)

Without the necessity of further detail, enough has been suggested to indicate the mechanism of the very delicate balance which must be established and maintained to assure normal functional and esthetic configuration of the dental arches. The introduction of extraneous forces, such as those in thumb- and finger-sucking, may, and not infrequently does, disturb this balance and alter the form of the dental arch. Whether this is a serious handicap to the person depends upon the likelihood that the displacement will be beyond the possibility of recovery through natural agencies in the interval when the detrimental forces are not active or have been discontinued.

The criterion of judgment lies in appraisal of the nature, the intensity, and duration of the external pressures when evaluated with the physiologic factors of the mechanism. If the habit produces a deformity which in its configuration resists recovery, as is the case with anterior locking of the upper as compared to the lower teeth or cushioning of the lower lip between the upper and lower anterior teeth, the possibility of spontaneous recovery is unlikely (Fig. 6). Likewise,



A.



B.

Fig. 6.—Illustrations of the relationship of the supporting tissues to the dental units. *A*, Normal balance of external and internal soft tissue pressures in the incisor region. (Reproduction from W. Spalteholz, Handatlas der Anatomie des Menschen, Vol. III, Leipzig, 1922, S. Hirzel.) *B*, Abnormal balance of these influences, perverting the functional factor and contributing to malocclusion.

if the habit serves to accentuate an abnormality arising from other causes, such as growth or respiratory disturbances, it must be considered as pernicious from a regional standpoint. It is unfortunate that this judgment cannot be reduced to axiomatic and rule of thumb criteria, but it rests upon a very comprehensive knowledge and appreciation of the anatomy and physiology of the area.

While it is sometimes true that the local deformity is preferable or unavoidable when the complete welfare of the child is considered, that is no excuse for ignoring the penalty which is being paid. In analysis of the problem, it is essential that the first determination be the actual influence of the habit. If it is found responsible for changes beyond the likelihood of recovery, the next consideration is the manner and advisability of its correction. There are some cases in which the deformity bears little or no relation to the habit; there are some in which it is intensified by it; there are others where it is the sole cause. In all of these there may be instances in which the cure may be spontaneous or contraindicated. Like many pediatric problems, the solution must entail a comprehensive appraisal of the child as a whole, and, in many instances, this taxes the experience and judgment of both the orthodontist and psychiatrist as well.

DR. W. S. LANGFORD.—Thumb- and finger-sucking is a frequent and important problem in pediatric practice because of the concern which it causes in parents. Frequently the sucking habit is accompanied by an accessory movement which takes the form of pulling the ear, twisting the hair, handling the genitals, or rubbing some soft fabric. With some children the accessory movement persists after the sucking is discontinued, or the accessory movement may replace the sucking, or it may be drawn into the act, as in the sucking of a wooly object.

The concern in parents seems to be due to the alarm spread in the last forty years by alarmists. It is important to know exactly what dental deformities may be caused and to what extent recovery is possible. Other effects have been attributed to the habits, as deformities of the fingers, scoliosis, or gastrointestinal upsets. It has been designated as a contributory cause of diseased tonsils and adenoids, and it has been said that changes in the facial expression, not related to bony deformity, may cause profound later character changes. It would seem that such changes are rather the result of the teasing and shaming the child receives as a result of his sucking which push him into a voluntary unsocial type of behavior. There is no evidence that thumb- and finger-sucking is a sexual activity, although certainly it is pleasurable and highly infantile in nature.

In clinical consideration it is convenient to divide the children into three age periods with regard to the occurrence and treatment of thumb- and finger-sucking.

In *infancy*, during the early months, sucking occurs as a result of a sucking reflex when the hand is brought in contact with the mouth. During the hand-to-mouth reaction period from the fourth to tenth months, until the tactile sensation is well developed in the hands, the mouth is used definitely as an exploratory organ. Levy's work tends to show that in certain infants sucking will occur as a result of insufficient sucking movements during the normal feeding period. It will also occur when the child is hungry or underfed. Treatment in this age period should consist of regulating the feeding activities to make sure that the child is receiving sufficient food and sucking stimulation, as well as assuring oneself that the feeding methods are not destructive. Often, when the child is receiving too little mothering or cuddling, a little more of this attention will serve to abolish abnormal sucking behavior. Restraints at this time are not very helpful, but they do not do the definite harm they do in the *preschool* period when they are apt to precipitate a power contest. During this second period thumb- and finger-sucking are apt to occur in situations when the child is bored, tired, frustrated, or ill. Deprivations and punishments also seem to precipitate sucking

behavior. A good deal of the irritability and frustration at this age period is unavoidable. In treatment one should eliminate the outstanding causes of emotional dissatisfaction in the child's life. Sporadic thumb- and finger-sucking is the rule in this age period, and one should not feel concerned unless the child indulges in this type of behavior more or less to the exclusion of his other activities. In *older* children the sucking is apt to occur mostly as a part-manifestation in a more or less general social and emotional immaturity. Adequate handling in this age period calls for a detailed study and broad program of personality and environmental readjustment.

DR. R. A. HIGGONS, Port Chester, N. Y.—In older children where restraints are not desired, how about the use of sharp point at the posterior upper surface of the central incisors?

CHAIRMAN NOYES.—This raises the question of definition of the term restraint. The placing of a mechanical device might be considered as a restraint in the performance of a habit, as much as the use of a mechanical appliance upon the thumb, finger, or arm. It need not, however, interfere with functional activities of arm or hand. There are two essential factors to be considered in its use: (1) the advisability of forcibly interrupting the habit, essentially a psychiatric problem; (2) the effect which a rigid appliance fastened to the teeth may have upon the growth of the dental arches. With respect to the latter, judgment must be based upon the period of growth of the dental mechanism during the interval the appliance is worn and the nature of the appliance. There are times in which it may be positively contraindicated because of its interference with the normal growth in arch width. Likewise, at the same time the appliance interferes with the placing of the thumb behind the upper incisor teeth, which is an abnormal pressure influence, it interferes with the placing of the tongue in the normal position in the mouth, which is a normal pressure influence. In those cases in which psychiatric approach may not be feasible and at periods in which there is no lateral growth in the dental arches, it may be used for short periods of time, but the establishment of normal tongue function must be assured following its removal.

DR. LANGFORD.—I agree with Dr. Noyes that there are many disadvantages to this type of restraint. It has been pointed out that persistent sucking in an older child is usually symptomatic of some underlying disorder, and in order to correct it one should be concerned with the general state of mental hygiene rather than a direct attack on the symptom itself. We have also seen rather severe feeding problems develop after the use of such a device.

DR. A. M. KOHN, Detroit.—What type of restraint is practicable because of parental anxiety when infants gain normally and seem satisfied?

DR. LANGFORD.—Splints do make it a bit harder for the infant to get his finger in his mouth. If one feels he must use them, elbow cuffs are probably the most satisfactory. I do not believe that any restraint should be used after the first year, and I can see no absolute necessity for them even at that time. Most infants stop of their own accord after the cessation of the hand-to-mouth period. I see no harm in doing nothing in the line of restraints if this is at all practicable. Of course, I realize the pressure to do something which the parent sometimes places on the pediatrician.

DR. H. P. FINE, Perth Amboy, N. J.—What about the treatment of deciduous teeth before the eruption of the permanent teeth?

CHAIRMAN NOYES.—The indications for treatment of malocclusion in either deciduous or permanent dentition are determined by the presence of conditions or relationships which interfere with normal growth and function. The restoration of dental relationships and arch form to within the limits of normal function is extremely important in the deciduous dentition because of the effect which it may have upon the functional factor in growth. Obviously, if the habit persists following correction by mechanical means, the teeth may again be moved into abnormal relationships.

DR. C. J. OCHS, Cincinnati.—Is there any advice on other sucking habits, such as the rubbing of lips, etc.?

DR. LANGFORD.—The same factors which have been discussed with relation to finger- and thumb-sucking enter into the other sucking habits. The general principles laid down would then also hold for these related disturbances.

DR. C. J. DERRICK, West Palm Beach, Fla.—Does the treatment of deciduous teeth prevent the normal eruption of the permanent teeth?

CHAIRMAN NOYES.—Orthodontic treatment in the deciduous dentition does not interfere with normal eruption of permanent teeth. It cannot be expected, however, to assure the normal eruption of a permanent dentition, although it may contribute to that end by the removal of abnormal relationships. Not infrequently the pressures exerted by an orthodontic appliance on the deciduous teeth hasten the absorption of their roots. This process, however, is not necessarily a disadvantage or a contraindication for treatment.

DR. G. WELDFELT, Highland Park, Ill.—What about the educational value of thumb-sucking?

DR. LANGFORD.—Several writers have stressed the so-called "educational" value of thumb-sucking. I believe a bit of it is inevitable, but sucking that occupies a fair share of the child's waking time is not usual and I do not believe it can be considered normal. Nursing and feeding, on the other hand, are of great importance in the development of the mother-child relationship.

DR. J. H. MURPHY, Omaha.—What about other habits associated with thumb-sucking, such as sucking on the pillow or garment? What about the actual pressure exerted? What about change in the maxilla or mandible?

CHAIRMAN NOYES.—It has been my experience that frequently there are other habits associated with thumb- and finger-sucking. These, as you mentioned, may be substitutions, such as the sucking of pillow or garment. There is another group usually associated with kinesthetic sensations, such as rubbing the nose, pulling the ear, or running the fingers along the blanket.

Pressures exerted by the associated or substituted sucking habits depend entirely upon the manner in which the habits are performed. As a rule, they are less disturbing from the standpoint of dental arch configuration because of the direction and amount of force utilized.

As I tried to indicate in my introductory discussion, the change in form of the maxillae or mandible is dependent upon the intensity and duration of the pressures which disturb the normal mechanism of balance, as well as the reaction of the local tissues to external pressure. The effect of the same stimulus varies in different persons in the same way that there is considerable variation in the response of patients to the mechanical pressures developed by an orthodontic appliance.

DR. H. J. MORRISON, Savannah, Ga.—How do urban and rural infants and children compare in the incidence of thumb-sucking?

DR. LANGFORD.—My experience is almost exclusively with urban children. I would believe that the rural child of runabout age would be less likely to develop untoward sucking responses because he is restrained less, has more opportunity for free, unhampered play, and his period of dependency upon the parents is not so likely to be prolonged.

DR. W. E. KEITER, Kingston, N. C.—Do negro children have sucking habits as often as white children?

DR. LANGFORD.—Among the urban group of children I have seen, sucking habits are just as frequent.

DR. HIGGONS.—Just what harm may be attributed to thumb-sucking?

CHAIRMAN NOYES.—Considered only from the standpoint of its effect upon the denture, thumb-sucking may so alter the configuration of the dental arches that normal masticulatory and lip function is impossible. It may, under conditions in which the effect upon the mechanism is less severe, produce noticeable changes which are within the limits of restitution either during the intervals when the habit is not practiced or when the habit has been discontinued. There are a few persons who have been able to indulge in thumb-sucking without interfering sufficiently in the normal pressures to cause any noticeable change in tooth or jaw relationships. Unfortunately, it is impossible, without careful study and continued observation of the particular child, to give general prognosis.

DR. LANGFORD.—Sucking is a very infantile type of sensory satisfaction. The child who does not develop sources of emotional satisfaction more appropriate to his age has much more difficulty in making adjustments to life, and other personality changes may well appear. I must again remind you that I am referring to persistent, excessive sucking activities.

DR. C. C. STEWART, Hanover, N. H.—Dr. Langford, do you feel that any other discouragement of these practices should be avoided, such as cutting the hair of children who suck and pull their hair, or removing the special object associated with the act?

DR. LANGFORD.—The hair pulling may exist as an accessory movement to the finger-sucking or persist after the sucking has ceased. We have observed several of these children. In all of them the hair pulling was resumed after the hair had grown again. The disorder can be relieved after ameliorating the underlying factors. Sucking blankets as a bedtime ritual and other similar practices, as a rule, are easier to prevent than to correct. If the object is forcibly removed, the child may take up something else.

DR. KOHN.—Do teething rings do any harm? What about the symptoms due to teething?

CHAIRMAN NOYES.—As commonly used, I do not believe that teething rings do any harm. It is, of course, possible, depending upon the nature of the object used and the way in which it is handled, to cause damage with them. The ease with which the erupting tooth penetrates the soft tissue overlying it varies greatly in the individual child. The pressure of resistant objects upon the soft tissue often hastens the cutting of the teeth. Where the tooth has considerable difficulty in penetrating the overlying tissue, it may be of advantage to resort to the old procedure of lancing the gum or rubbing the teeth through. While

this was carried to excess in the past, it is decidedly better than to permit a long delay and discomfort in the cutting of the teeth.

The usual symptoms in teething are salivation and irritability. While teething is a normal physiologic function, the excessive salivation or the irritation of the child, together or singly, may disturb other physiologic activities, particularly those concerned with digestion. As the adult's digestive process may be disturbed in periods of irritability and nervous excitement, the same may be true with the infant. The resulting gastrointestinal dysfunction may be responsible for lowered resistance, resulting in infection. Teething itself, except in the rare instances where there is submucous hemorrhage, is not the direct cause of fever, but it may be an indirect contributing factor.

DR. F. W. LATHROP, Plainfield, N. J.—As a comment on Dr. Levy's theory, many Norwegian children are spoon-fed, never getting bottle or breast; yet thumb-sucking is said to be rare.

DR. LANGFORD.—That is quite interesting. Dr. Levy points out that there are large variations of the sucking need in different persons. The same observations have been made in calves and in the pecking behavior of chickens.

DR. KEITER.—In what percentage of cases of malocclusion is thumb-sucking an important factor?

CHAIRMAN NOYES.—I do not believe there are available any satisfactory statistical data covering the number of cases in which thumb-sucking is an important factor. While it is certain that its contribution was overestimated in the past, it is likely that it is being underestimated at the present time. A summary of the literature by Leland Johnson in a recent number of the *Journal of the American Dental Association* gives the incidence of thumb- and finger-sucking in children with malocclusion as 17 per cent.*

COMPARISON OF FINDINGS OF FOUR INVESTIGATIONS*

INVESTIGATOR	CASES STUDIED	NUMBER WHO SUCKED THUMB OR FINGERS	THUMB-SUCKERS AND FINGER-SUCKERS (%)
Hellman	354	90†	29.03†
Lewis	170	41	24.1
Lewis	131	36	27.48
Johnson	989	173	17.49

†Includes lip- and tongue-suckers as well as thumb- and finger-suckers.

DR. B. B. BREESE, Rochester, N. Y.—In the preschool child who sucks his thumb, what percentage of "cure" of the habit is obtained by psychologic approach, and how long does it take?

DR. LANGFORD.—This is another "all depends" question. It depends upon the factors operating to produce the habit and the degree of cooperation from the family, which may be poor because of the part the parents' personalities play in the development of the sucking. I would say that in most cases we get quite satisfactory results. The time involved may vary a great deal. Some cases are dramatic, the activity stopping after the first visit; in others, there are months of patient work before anything happens.

DR. G. HOEFFEL, Boston.—I would like to ask Dr. Noyes at what time in the case of the persistent thumb-sucker with malocclusion is the orthodontist willing to assume the responsibility of assisting the child, parent, and pediatrician in breaking the habit?

*Leland R. Johnson: Status of Thumb Sucking and Finger Sucking. Table 4. J. A. D. A. 26: 1245, 1939.

CHAIRMAN NOYES.—The time at which the orthodontist may utilize mechanical means in the correction of malocclusion due to thumb-sucking is the time at which alteration in the dental architecture has passed beyond the likelihood of recovery through normal functional forces. The decision to institute orthodontic treatment should be in corroboration with the pediatrician or psychologist, taking into consideration the psychiatric background of the child. This age varies from 2½ to 3 years up to or beyond adolescence.

DR. STEWART.—Dr. Langford, do you feel that babies should be allowed a bottle longer than they often are, in order to avoid interference with instinct satiation?

DR. LANGFORD.—Again a question where it "all depends," this time on the baby. If the bottle is removed and sucking activity increases, then it seems best to return the bottle. We have seen some children of 5 or 6 months take to the cup without developing any sucking habits, and others of a year begin to suck when the bottle is taken away.

DR. BREESE.—Is it possible to tell, in observing the individual child who is sucking his thumb, if malocclusion will result?

CHAIRMAN NOYES.—There is nothing certain but death and taxes. As previously stated, it is often difficult to tell whether malocclusion will or will not result from the habit. The orthodontist is assisted materially by opportunity to observe the child at intervals during which the habit is practiced. He may have reasonable certainty of an enduring deformity if the normal interdigitation of the dental units in the lateral segments of the dental arch is disturbed or if sufficient deformity has developed to permit the cushioning of the lower lip between the upper and lower incisors.

DR. G. F. PATTERSON, Cincinnati.—Is there any greater proportion of thumb-suckers in family groups where there is one child, than in families where there are more than one child?

DR. LANGFORD.—From my experience, I would say no. I do not know what the experience of others is.

DR. HOEFFEL.—In the practical approach to the problem of rather late and persistent thumb-sucking, would you recommend that the pediatrician resort solely to the psychologic and condemn the mechanical treatment?

DR. LANGFORD.—Many do not feel it is necessary until after the first year of life. I believe that even then the adjustment of the child's general schedule, feeding and the like, is more satisfactory than the use of splints.

CHAIRMAN NOYES.—While there are undoubtedly instances in which mechanical methods may be indicated, as a generality I believe that the psychologic approach is the most satisfactory.

DR. KEITER.—Do you use chewing gum as a substitute for the sucking habit?

DR. LANGFORD.—I have tried it. Sometimes it works and sometimes it doesn't. Lollypops have also been advocated as being useful. Neither should be used as the only means of trying to help the child.

DR. MAX DEUTCH, St. Louis.—Will Dr. Noyes comment on mechanical help, if any, from chewing gum in cases of malocclusion?

CHAIRMAN NOYES.—The chewing of gum is usually of little assistance in correction or prevention of malocclusion because: (1) most of the gums used are too soft to exert any very positive pressure on the teeth; (2) where malocclusion has shifted the occluding surfaces of the teeth beyond limits of normal interdigitation, whatever force is exerted tends only to lock them more firmly in their abnormal positions. The chewing of more resistant material, such as rubber, has a far more stimulating effect upon the supporting tissues. Likewise, the lateral movements of mastication are more advantageous than the vertical or chopping movements.

DR. J. B. BILDERBACK, Portland, Ore.—Do primitive races have sucking habits?

DR. LANGFORD.—I couldn't say. I am not familiar with that aspect of the literature.

Oliver L. Stringfield, M.D., Stamford, Conn.

REPORT OF THE COMMITTEE ON IMMUNIZATION AND THERAPEUTIC PROCEDURES FOR ACUTE INFECTIOUS DISEASES

MAY, 1940

Chemotherapy in Acute Infectious and Contagious Diseases

A. Drugs Recently Introduced

(1) Sulfanilamide; (2) sulfapyridine; (3) monohydrate sodium sulfapyridine; (4) neoprontosil; (5) several drugs being investigated—sulfathiazole, sulfamethylthiazole, and promin.

B. Terminology and Dosages

1. Sulfanilamide

Known as paraaminobenzenesulfonamide; prontosil album; prontylin; colsulanyde; deseptyl; 1162 F; stramid; streptocide; sulfamidyl; sulphonamide (or sulfonamide) P. Sold in tablets or capsules, 0.32 Gm. (5 grains) and 0.48 Gm. (7.5 grains), or as a crystalline powder. Given subcutaneously, intramuscularly, intravenously, intrathecally, rectally, and orally. Intrathecal injections have been generally abandoned. It is best given by mouth, by stomach tube, or subcutaneously if necessary. The blood level should be about 10 mg. per cent. Accepted by the American Medical Association. In the United States Pharmacopeia.

Dosage.—Initial dose is amount equivalent to one-half total first day's dose; first day's dose, 1 grain (0.065 Gm.) per pound up to 120 pounds (54.5 kg.); second day's dose, ½ grain (0.030 Gm.) per pound up to 120 pounds (54.5 kg.) in divided doses; third day's dose, same as second day's. Stop if possible. Proceed cautiously. (Dose for infants, 50 per cent more; children, 25 per cent more.) Blood and urine examination daily. Sulfanilamide for injection is made up by slowly dissolving 1 Gm. of the crystalline powder in 100 c.c. of warmed Hartmann's solution.

2. Neoprontosil

Known as prontosil; prontosil soluble; prontosil S; prontosil solution; streptozon; streptozon S. Sold in capsules, 0.2 Gm. (3 grains); tablets, 0.3 Gm. (5 grains); or solution (2.5 to 5 per cent ampules). 100 c.c. of a 2.5 per cent solution = 11 grains (0.665 Gm.) sulfanilamide. Not accepted by the Council on Pharmacy and Chemistry of the American Medical Association. The tablets or capsules can be ingested and the solutions injected as purchased.

Dosage.—First day, 60 to 80 grains (4 to 5⅓ Gm.); second day, 15 to 20 grains (1 to 1⅓ Gm.) q. 4 h.

3. Sulfapyridine

Known as sulfanilamide-pyridine; sulfone-pyridine; pyridine sulfanilamide compound; dagenan; M & B 693. Sold in tablets and capsules, 0.25 Gm. (3¾ grains) and 0.5 Gm. (7½ grains). It is given by mouth and is very insoluble. The blood level should be from 4 to 10 mg. per cent.

Dosage.—Adults are given 2 Gm. (30 grains) stat., then 1 Gm. (15 grains) q. 4 h. until the temperature in normal, usually the third day. Try to stop when 25 Gm. (375 grains) have been given. Children up to 10 years get ½, infants up

to 6 months, ⅛ to ¼, and infants from 6 months to 1 year ¼ to ½ of adult doses. Pneumonia in children often responds to intensive treatment within forty-eight hours and the drug can be stopped sooner. In severe fulminating infections, an initial dose equal to the whole twenty-four-hour dose may be given on admission. In influenzal and staphylococcic meningitis or staphylococcic septicemia, massive doses may be given the first few days, enough to bring the blood and spinal fluid levels up to from 20 to 30 mg. per cent. Absorption is erratic at times, and dosages may have to be changed to bring the blood concentration up to a proper level. Blood and urine examinations must be done daily. Give transfusions if anemia develops.

4. Sodium Sulfapyridine Monohydrate

Sodium sulfapyridine monohydrate is a very soluble salt of sulfapyridine. Sold in 2 Gm. (30 grains) and 4 Gm. (60 grains) ampules and 5 Gm. (75 grains) vials.

Dosage.—0.06 Gm. (1 grain) of the drug per kilogram of body weight in 5 per cent sterile distilled water. Blood levels should not be less than 4 and not over 20 mg. per cent. Blood and urine examinations to be made daily. Accepted by the American Medical Association.

C. Uses

1. Sulfanilamide

Sulfanilamide is the drug of choice for all beta-hemolytic infections (Lancefield types A-K, especially A, and probably B and G).

Sulfanilamide is used in infections due to *Streptococcus hemolyticus*, such as adenitis, Ludwig's angina, suppurative arthritis, bacteriemia, cellulitis, erysipelas, mastoiditis, streptococcic pneumonia (measles, whooping cough), meningitis (streptococcic), osteomyelitis, otitis media, peritonitis, pharyngitis, puerperal sepsis, scarlet fever complications, sinusitis, tonsillitis; it is also used in undulant fever, meningitis (meningococcic), urinary infections, secondary infections accompanying smallpox, chicken pox and impetigo, and in gonorrheal infections of all types.

2. Neoprontosil

Neoprontosil has no marked advantage over sulfanilamide, but it may be used when the other drugs cannot be given. It is sometimes recommended in ulcerative colitis. The drug is excreted in the urine which stains the bedclothing pink.

3. Sulfapyridine

Sulfapyridine is the drug of choice in the treatment of pneumococcus infections; it is the one to be tried when the causative bacteriology is doubtful and in staphylococcic infections, etc. It may be used in gonorrheal infections of all types.

4. Sodium Sulfapyridine Monohydrate

Sodium sulfapyridine monohydrate is given only intravenously and where other drugs cannot be given, or if there is delay in absorption. CAUTION: Never inject anywhere outside the vein. This is a valuable, but dangerous, drug.

D. Complications

1. Following the Use of Sulfanilamide

Malaise; headache; anorexia; nausea; diarrhea; constipation; vomiting; abdominal pains; hepatitis; lassitude or weakness; depression; mental confusion; inability to concentrate; vertigo; tinnitus; paresthesia; peripheral neuritis; difficult micturition; dyspnea; lowering of CO_2 combining power; cyanosis; fever; cutaneous rashes of morbilliform, scarlatiniform, urticarial, or purpuric types; heliosensitivity; pruritus; dermatitis; jaundice; hemolytic anemia; granulocytopenia. The blood picture must be followed. Some believe that, if a drop in hemoglobin and leucocytes occurs, toxic destruction is indicated, and that the use of the drug should be stopped

and not resumed; however, where the outcome seems hopeless, as it often is with many infections, one is justified in again giving the drug and, at the same time, frequent blood transfusions.

2. Following the Use of Sulfapyridine

All those complications listed under "Sulfanilamide," plus the finding of crystals and red and white blood cells in the urine; a decrease in the total number of red blood cells and the hemoglobin content of the blood; blood urea nitrogen retention; renal calculi.

E. Other Drugs

1. Sulfathiazole

This drug is being used experimentally in many clinics. It has been claimed that nausea is absent or less frequent following its use than is the case with sulfapyridine. This is not the experience of all members of the Committee. As far as is known, it has no advantage over sulfapyridine in the ordinary infections where sulfapyridine has been used previously. It might be superior to other drugs in the treatment of staphylococcus infections, but the evidence is not at hand to support this conclusion. One should continue to use sulfapyridine until more is learned about sulfathiazole.

The same complications follow its use as those that occur when other chemotherapeutic drugs are employed.

2. Sulfamethylthiazole

This drug has been used experimentally in many clinics. It has no advantage over sulfapyridine or sulfathiazole. It may possibly have greater disadvantages. From one clinic it has been learned that the use of this drug has been accompanied by peripheral neuritis. At least one manufacturer has withdrawn the material, even from clinical investigation, until further notice.

The physician should not use this drug in private practice without great caution. It would be better to await further reports regarding its safety.

3. Promin

This drug has been tried clinically, and, from the evidence at hand, has definite possibilities. It has been used mostly in streptococcus infections; it does not cause destruction of hemoglobin or white blood cells in the dosages recommended. It can be used in massive amounts, but must be injected intravenously.

This drug, to our knowledge, has not as yet been formally presented to the Council on Pharmacy and Chemistry.

John A. Toomey, Chairman
Horton Casparis
E. J. Huenekens
Charles F. McKhann
Béla Schick
Edward B. Shaw

Academy News

Dr. Alfred James Scott, Jr., of Los Angeles, died April 17, 1940. Dr. Scott was Professor Emeritus of Clinical Pediatrics at the College of Medical Evangelists. He was a past president of the Southwestern Pediatric Society and an Emeritus Fellow of the American Academy of Pediatrics.

The American Academy of Pediatrics has entered into a contract to have certificates of membership mounted in a practically indestructible plaque, the cost of which will be one dollar to each member. Any member wishing his certificate so mounted should send the certificate, together with a check for one dollar, to the secretary.

News and Notes

The twenty-fifth anniversary of the founding of the Uruguayan Society of Pediatrics was held in Montevideo, April 26 and 28. Delegates from many American countries attended, Argentina, Chile, Ecuador, and the United States being among those represented. Many of the delegates came by boat from Buenos Aires, and Uruguayan hospitality began with an enthusiastic reception at the pier in Montevideo.

An impressive memorial service was held at the base of the beautiful bronze statue of Morquio in the Park of the Allies. Floral pieces and short tributes were made to Morquio's genius and influence. From here the delegates were taken to a new pavilion for the polyclinic of the Hospital Pereira-Russell. Built on modern lines, the building allows great efficiency of service and pleasing architectural form.

The first scientific program was presented in an auditorium on the same grounds. Professor Arana and Dr. Kreutzer of the Children's Hospital of Buenos Aires presented a study of electrocardiograms in diphtheria.

The formal convocation was held in the large auditorium of the Faculty of Medicine, with presidential words of honor. The Secretary of the Interior, officers of the Uruguayan Society, and the delegates were presented to a large group of professional and lay people. Brief responses from the delegates praised the splendid pediatric program of Uruguay and urged cooperation, exchange, and understanding between the respective republics. Following the convocation, the official banquet was held at one of the large hotels. About 500 were present.

On Saturday morning a second scientific program was given in the amphitheater of the Hospital Visca. Studies concerning the etiology of infectious diarrhea in infants were reported by Dr. Bonavu, Dr. Carran, and others. It would appear that salmonella may be of increasing significance as an etiological agent.

The entire group then visited the country farm which cares for dependent minors. This is one of many of the splendid social programs characteristic of Uruguay. The boys are housed as family groups of from fifteen to twenty persons in the custody of a farmer and his wife. The boys learn farming, as well as certain trades, and receive regular schooling. Individualization is made possible by aptitude and psychology studies.

The final scientific session was held Saturday afternoon in the new Institute of Hygiene. This splendid structure of marble and stone was built at great cost, and no expense was spared in equipment and appointments. Near by is the new M. S. building, a structure, of some twenty stories, nearing completion. Both these buildings are removed from the center business district to a beautiful open site overlooking the large Park of the Allies.

That night a delightful reception for the delegates was held in the home of Dr. and Señora Bonavu.

On Sunday a long trip brought the parties to a semimountainous region famous for its mineral springs. The entire group attended a cocktail party that evening when Dr. Pelford, chairman of the convention, and Mrs. Pelford were hosts in their lovely old home. Laden with gifts and happy memories of delightful hospitality, the guests were escorted to the boat. *Viva el Uruguay. Hasta luego!*

F. S. S.

Book Reviews

Dentistry for Children. John Charles Brauer, D.D.S., with special chapters by L. B. Higley, D.D.S., and Julian D. Boyd, M.D. York, Pa., 1939, Maple Press Company. Pp. 373.

Dr. Brauer is head of the Department of Preventive Dentistry, professor of Pedodontics, and director of the Bureau of Dental Hygiene at the University of Iowa School of Dentistry. Dr. Higley is professor and head of the Department of Orthodontics of the School of Dentistry, University of Iowa. He has written a chapter on preventive orthodontia and minor oral surgical procedures for children. Dr. Boyd is associate professor of Pediatrics at the University of Iowa School of Medicine and has written chapters on growth and development of the normal child, principles of nutrition, and the nature of disease during childhood. Dr. Boyd has recorded an interest in dentistry for children, has written extensively in pediatric and dental literature on dental subects, indicating the nutritional aspects of children's teeth and also the evidence in the teeth of general nutritional states, especially diabetes and dental caries.

The book is devoted entirely to dentistry for children. There is a satisfactory chapter on preventive dentistry and an important one on growth and development of teeth, one on management of the child, and an interesting one for pediatricians concerned with the "Business Side of Pediatrics," telling about appointments and business fundamentals. It is not often that reference is made to this subject in medical books—perhaps not often enough.

The section devoted strictly to the main subject by the principal author is a detailed and satisfactory explanation of dental procedures. It may not be easy or desirable for pediatricians to criticize correctly such procedures, but they should be familiar with the subject and should be able to discuss it intelligently with parents. This field is distinctly within the sphere of pediatric influence.

The book is profusely illustrated; the subject material is easily readable. Its form is rather unusual in the style of type and arrangement, and there is obvious need for severe editorial revision. References to the literature are extensive, but there is a marked deviation from the standard reference form.

The important subject of dental caries in children is still a debatable one and is not settled in this volume, but the evidence is increasing that oral bacterial flora are of secondary importance, and that the tooth, like any other part of the body, is subject to the same influences of growth, development, nutrition, injury, and repair as any other tissue.

There is an inadequate discussion of orthodontia and its relation to pediatrics. This growing field of dentistry is important to the pediatrician, probably equal to that of dental caries. Even with its few defects, which are correctable, the book is a valuable edition to the pediatrician's "tool shelf."

Congenital Cleft Lip, Cleft Palate, and Associated Nasal Deformities. Harold Stearns Vaughan, M.D., D.D.S. Philadelphia, 1940, Lea & Febiger. Pp. 210.

The author is professor of Clinical Surgery at Columbia University at the New York Post-Graduate Medical School. The book is written for the general surgeon, the pediatric surgeon, and the specialist in plastic and reconstructive surgery. For the general pediatrician, there is an important chapter on embryology, anatomy,

and physiology of the structures related to cleft lip and palate; a chapter on etiology and incidence; and one of special pediatric interest on the physiology of speech and deglutition, both in normal persons and in patients with cleft palate. The remainder and major portion of the volume is devoted to surgical problems.

The book is well written and illustrated. It is somewhat brief. There is a good bibliography, and it is sufficiently inclusive. It will fill a distinct need which may arise occasionally in pediatric practice.

Functional Disorders of the Foot. Frank D. Dickson, M.D., and Rex L. Diveley, M.D. Philadelphia, 1939, J. B. Lippincott. Pp. 305. Price $5.

No better review of this book could be presented than a restatement of its preface. Only one portion may be given, however, and that one which indicates the pediatric interest. The material "deals chiefly with the clinical aspect of foot disorders. Only such material on the evolutionary development of the foot, on anatomy, and on physiology has been introduced as seemed necessary to an intelligent understanding of the foot as a functioning organ and to an appreciation of those departures from normal which cause painful and incapacitating conditions. Its aim has been to present a practical and perhaps elementary statement of the cause and symptoms of disabling foot conditions and to suggest such therapeutic measures as have proved useful in pathology or relieving symptoms.

"It has seemed desirable to dwell at some length upon the foot of childhood and adolescence, as many of the faults in foot architecture which produce symptoms in the adult have their origin in the growing foot of the child and the developing foot of the adolescent period. As much more can be done to architectural faults responsible for the development of functional foot disorders between the ages of 2 and 16 years than after the adult age has been reached, this period of foot development seems worthy of careful study. This method of approaching the subject has resulted in a certain amount of repetition in discussing etiology, symptomatology, and treatment, but it seemed best to make each section as complete and self-contained as possible."

As one analyzes the book, pediatric features become obviously the dominant ones and make the book of extreme value to every pediatrician. There is no more important field of pediatric practice. Subjects of this kind make pediatrics a specialty, but it is safe to say that few pediatricians are really informed correctly on this particular problem. The book should be required reading for pediatric licentiates.